Interstitial Lung Diseases

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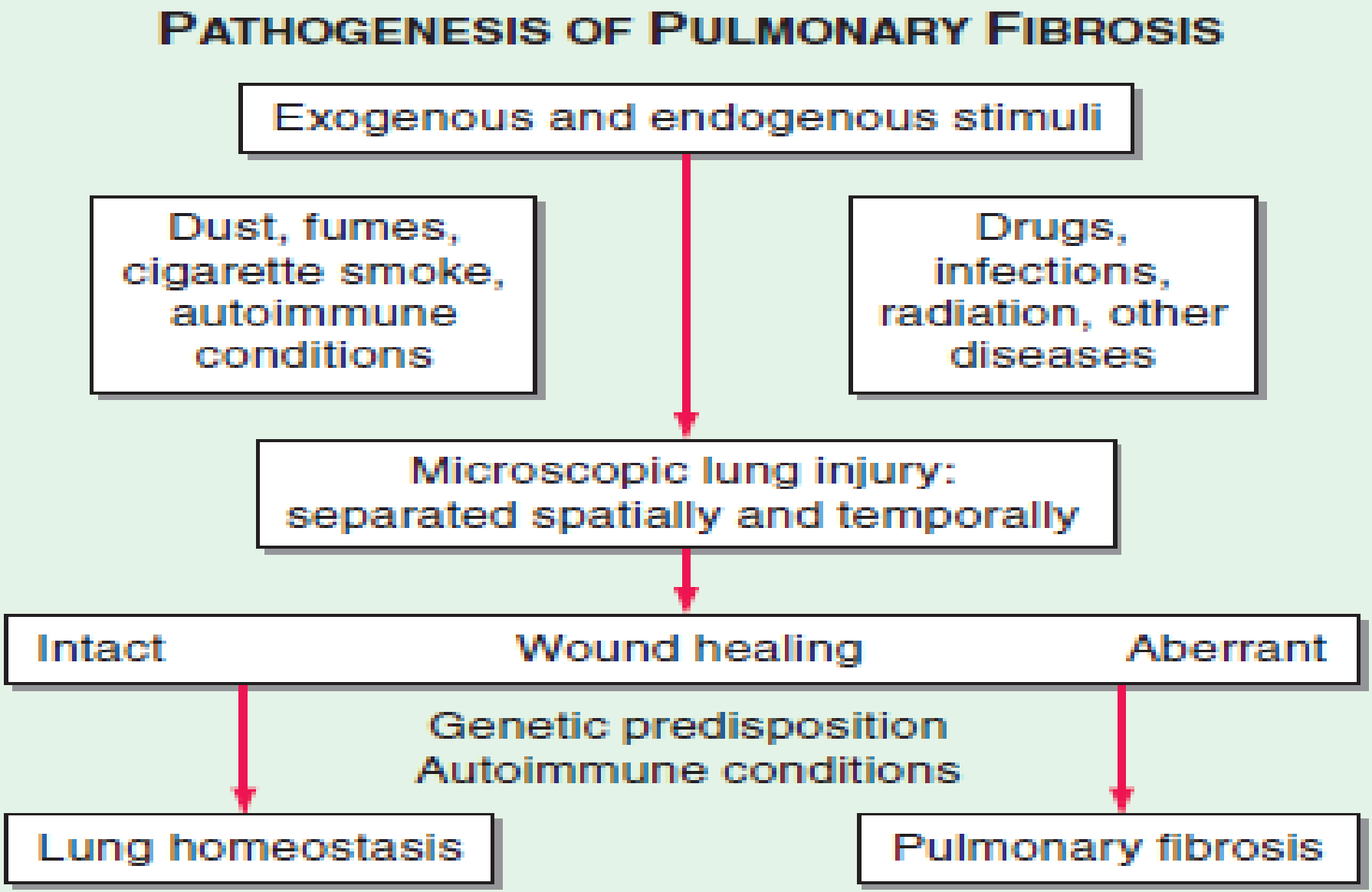
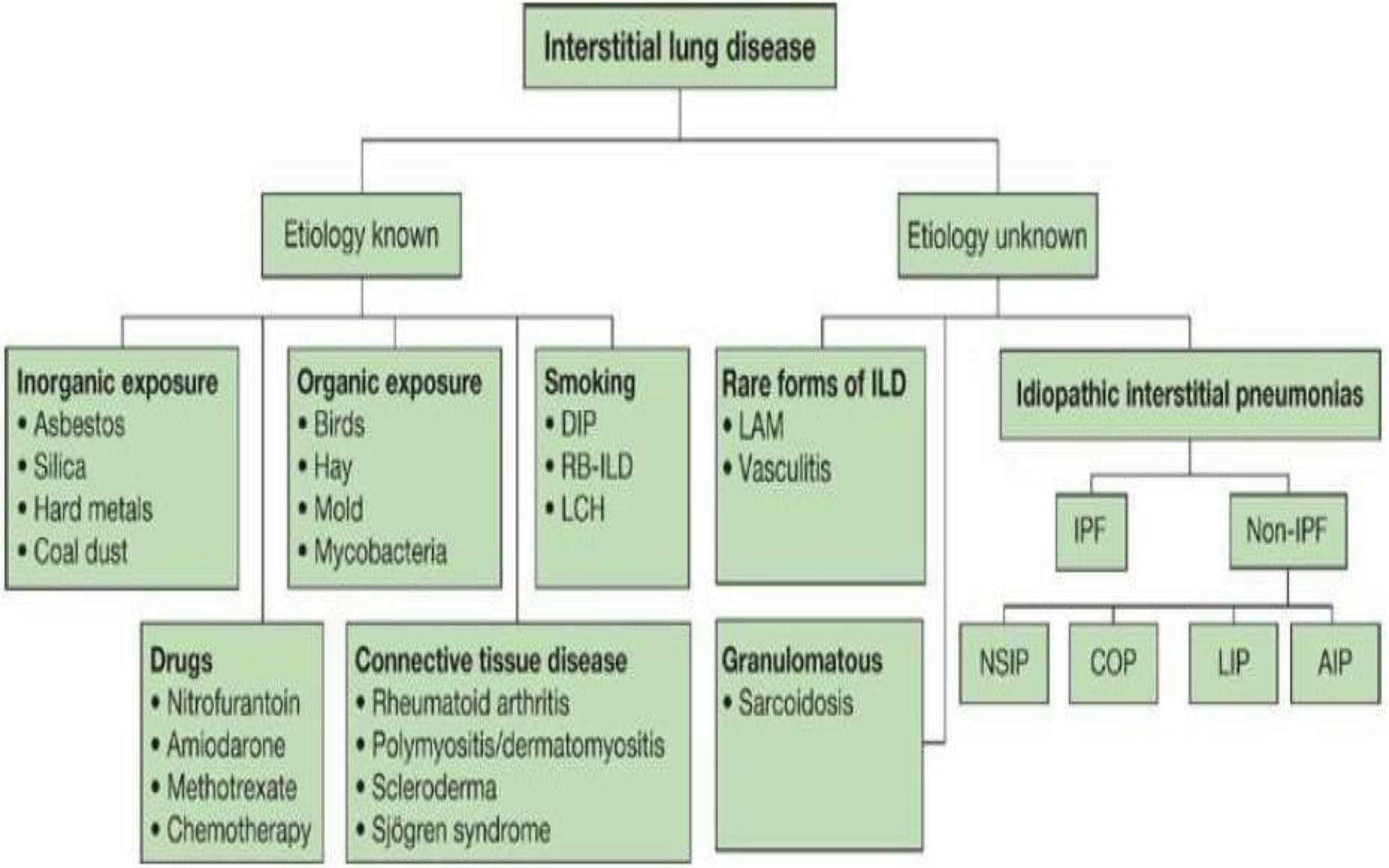
Definition and Epidemiology

- Definition
- ILDs represent a large number of conditions that involve the parenchyma of the lung—the alveoli, the alveolar epithelium, the capillary endothelium, and the spaces between those structures—as well as the perivascular and lymphatic tissues. The disorders in this heterogeneous group are classified together because of similar clinical, roentgenographic, physiologic, or pathologic manifestations
- Epidemiology
- Uncommon in compare with asthma ,COPD
- True prevalence is unknown ,IPF is the most common

Pathogenesis



classification



Evaluation of pt with ILD

Clinical evaluation

- Typical presentation of ILD is nonspecific
- Dyspnea on exertion and non productive cough are the most common presenting symptoms.
- mostly subacute to chronic onset .
- History
- Three main questions require answering from the history:
  - 1. What is the natural history/chronology of the condition to date?onset and course
  - 2. Are there any respiratory risk factors/aetiological agents?
  - 3. What is the severity of the symptoms

History

- Duration of Illness
- In most ILDs, the symptoms and signs form a *chronic presentation* (months to years)
- Acute presentation (days to weeks), although unusual, occurs with allergy (drugs, fungi, helminths), acute interstitial pneumonia (AIP), eosinophilic pneumonia, and hypersensitivity pneumonitis. These conditions may be confused with atypical pneumonias
- Episodic presentations are unusual and include eosinophilic pneumonia, hypersensitivity pneumonitis, COP, vasculitides, pulmonary hemorrhage, and Churg-Strauss syndrome.

Respiratory symptoms

- Cough
- Cough is usually an ‘‘airway-centred’’ symptom which is more likely in bronchocentric diseases such as sarcoidosis, HP and COP. A dry cough is also common in IPF. Productive cough occurs when there are excessive secretions in the tracheobronchial tree—for example, associated with chronic bronchitis or bronchiectasis coexisting with ILD.
- Dyspnea is a common and prominent complaint in patients with ILD,more on exersion

Respiratory symptoms

- Wheezing is an uncommon manifestation of ILD but has been described in patients with chronic eosinophilic pneumonia, Churg-Strauss syndrome, respiratory bronchiolitis, and sarcoidosis.
- Clinically significant chest pain is uncommon in most ILDs. Pleurisy suggests connective tissue disease (especially rheumatoid arthritis and systemic lupus erythematosus), asbestos related disease and drug-induced lung disease However, substernal discomfort is commonin sarcoidosis. Sudden worsening of dyspnea, especially if associated with acute chest pain, may indicate a spontaneous pneumothorax, which occurs in PLCH, tuberous sclerosis, LAM,.

Respiratory symptoms

- Frank hemoptysis and blood-streaked sputum are rarely presenting manifestations of ILD but can be seen in the diffuse alveolar hemorrhage (DAH) syndromes, LAM, tuberous sclerosis, and the granulomatous vasculitides.
- Haemoptysis in IPF should alert the clinician to the possibility of a complication such as lung cancer, pneumonia or pulmonary embolus
- Fatigue and weight loss are common in all ILDs

History

- Age :Most patients with IPF are older than 50 years, sarcoidosis, ILD associated with CTD, lymphangioleiomyomatosis (LAM), present between the ages of 20 and 40 years.
- Gender

IPF and pneumoconioses are more common in men while LAM and pulmonary involvement in tuberous sclerosis ILD in CT diseases more in female.

- Family history

A positive family history of respiratory disease should be sought. Both sarcoidosis and IPF may be familial.

History

Respiratory risk factors

- Smoking

respiratory bronchiolitis interstitial lung disease (RBILD), desquamative interstitial pneumonia (DIP) and Langerhans' cell histiocytosis (LCH) occur almost exclusively in smokers. Smoking is an independent risk factor for IPF and Goodpasture's syndrome .

- Occupation

A detailed occupational history needs to be taken

- Hobbies/environment/travel.

Travel may raise the possibility of eosinophilic lung disease secondary to parasite infestation.

History

- Rheumatological symptoms

may point to a specific underlying rheumatological diagnosis. In particular, enquiries should be made about Raynaud's phenomenon, skin thickening, dysphagia and acidreflux, arthralgia, rashes, ocular symptoms, sicca symptoms (dry eyes and mouth), myalgia and proximal muscle weakness.

In addition, information on constitutional symptoms of fever,sweats, malaise and weight loss should be sought.

- HIV risk factors

This is particularly important in acute onset ILD, which may represent opportunistic infection.

History

Past medical history

- Previous history may suggest a particular ILD, eg, haematuria (vasculitis), asthma/rhinitis (Churg-Strauss syndrome) or a previous malignancy that may have been treated with chemotherapy or radiotherapy. Although radiation pneumonitis usually develops within a few weeks or months of treatment,
- pulmonary fibrosis may evolve and present several months or years later.
- A history of pneumothorax may suggest cystic lung disease associated with LCH or lymphangioleiomyomatosis (LAM).

History

- Drug history
  - It is vital to obtain a detailed history of all previous drug therapy including intermittent courses of drugs. This should include dose and duration of treatment as some drugs are toxic because of the cumulative dose.
- Assessment of disease severity

This should include an assessment of exercise tolerance on both the flat and on increased exertion (eg, walking up stairs or inclines).

examination

General examination

- ✓ Tachypnea and cyanosis
- ✓ Clubbing is suggestive of IP, asbestosis chronic HP or rheumatoid arthritis with ILD.
- ✓ The presence of peripheral stigmata of systemic disease, usually connective tissue or rheumatological disease. rheumatoid arthritis (symmetrical deforming arthropathy of the hands, rheumatoid nodules)

systemic sclerosis (tight and shiny skin, telangiectasia, sclerodactyly,)SLE (petechial rash, livedo reticularis, purpura, arthropathy. butterfly skin rash)

dermmyositis (Gottron's papules, htdiotrope rash)

LOCAL EXAMINATION

- Usually, there is symmetrical involvement of the lungs, thus trachea is central,
- .reduced expansion generally or localized .
- The bases are often associated with a dull percussion note, reduced vocal or tactile fremitus and reduced air entry.
- fine end-inspiratory crackles are the whole mark in most ILD
- Bronchial breathing in cases of apical fibrosis.
- Inspiratory squawks may be present in (bronchiolitis)
- wheezing or bilateral rhonchi may be heared .

Investigations

Laboratory investigations

- Full blood count: lymphopenia in sarcoid; eosinophilia in pulmonary eosinophilias and drug reactions; neutrophilia in hypersensitivity pneumonitis
- Ca^{2+}: may be elevated in sarcoid
- Lactate dehydrogenase: may be elevated in active alveolitis
- Serum angiotensin-converting enzyme: non-specific indicator of disease activity in sarcoid
- ESR and CRP: non-specifically raised
- Autoimmune screen: anti-cyclic citrullinated peptide (anti-CCP) and other autoantibodies may suggest connective tissue disease

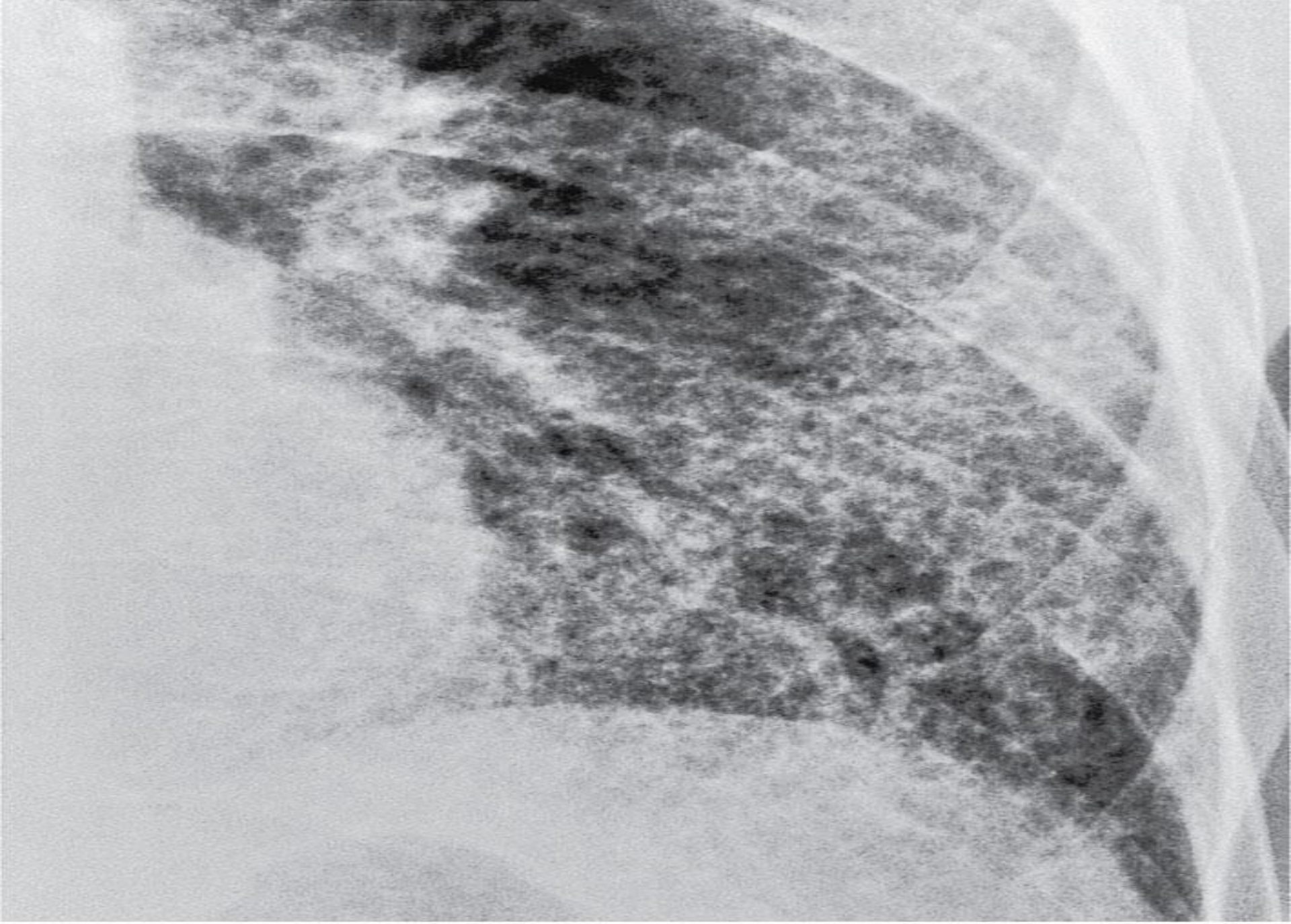
Investigations

Radiology

- Chest X-ray: typically small lung volumes with reticulonodular shadowing but may be normal in early or limited disease
- HRCT: combinations of ground glass changes, reticulonodular shadowing, honeycomb cysts and traction bronchiectasis, depending on stage of disease

Pulmonary function

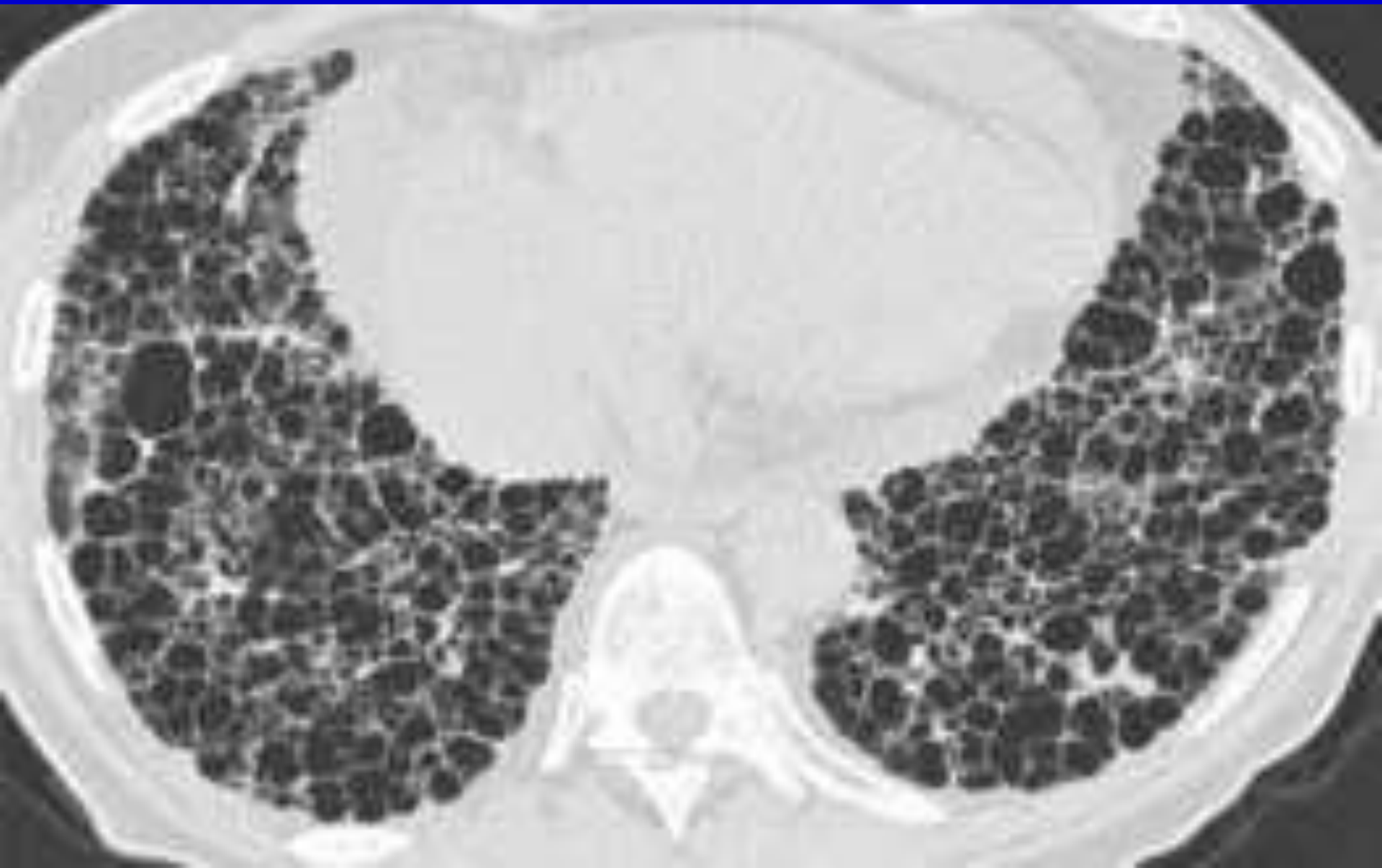
- Typically restrictive ventilatory defect with reduced lung volumes and impaired gas transfer; exercise tests assess exercise tolerance and exercise-related fall in SaO_2

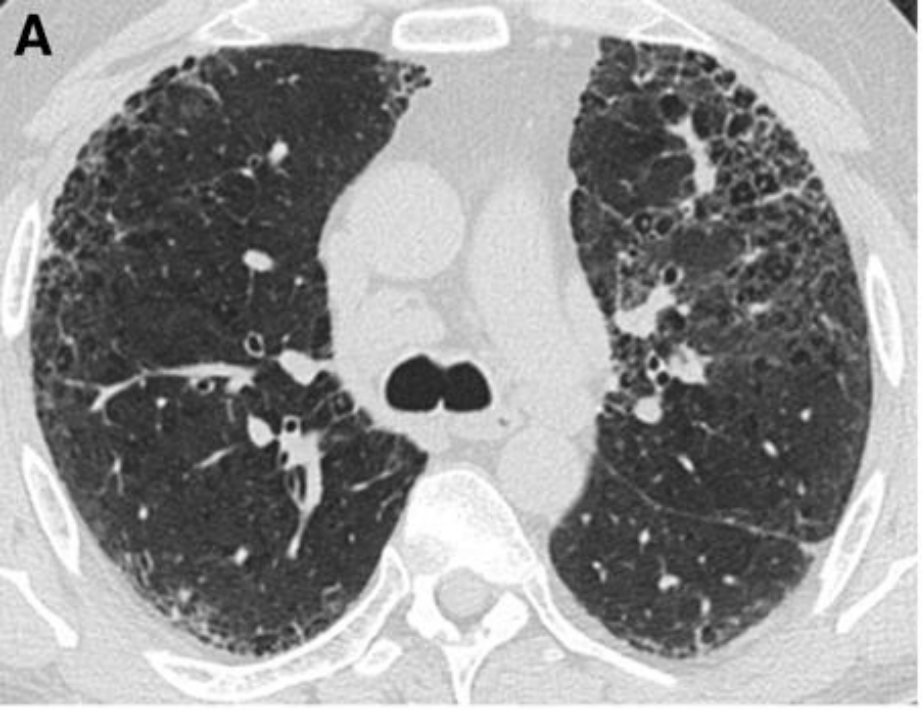


(From Hansell DM, Armstrong P, Lynch DA, McAdams HP, eds: *Imaging of diseases of the chest,* ed 4, Philadelphia, 2005, Elsevier.)

Fig. 25-2. Reticulonodular pattern of interstitial pulmonary fibrosis in a patient with scleroderma.

Radiology

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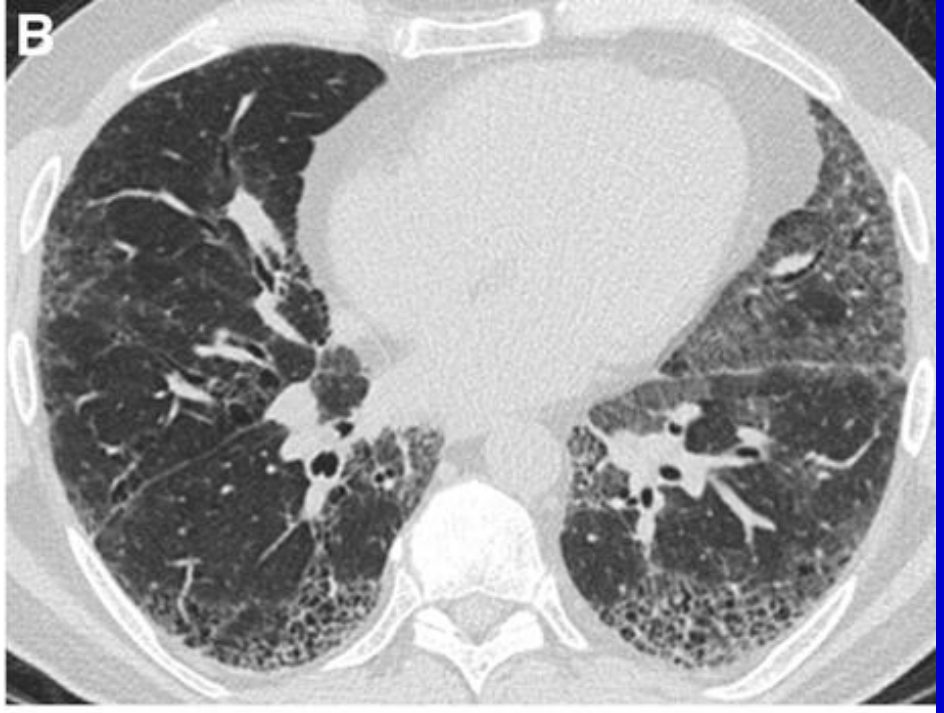
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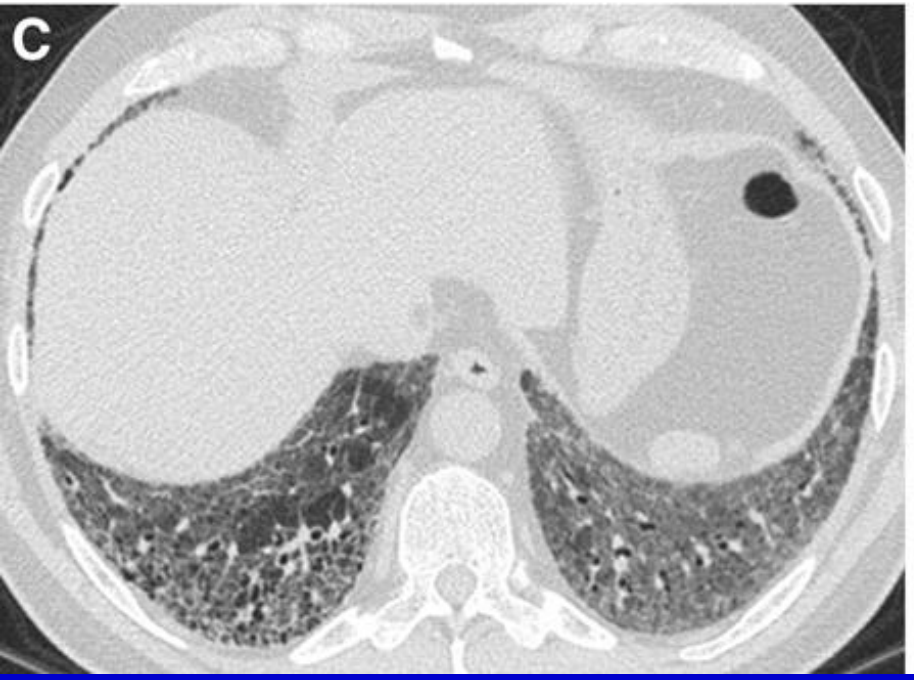
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Bronchoscopy

- Bronchoalveolar lavage: differential cell counts may point to sarcoid and drug-induced pneumonitis, pulmonary eosinophilias, hypersensitivity pneumonitis or cryptogenic organising pneumonia; useful to exclude infection
- Transbronchial biopsy: useful in sarcoid and differential of malignancy or infection
- Bronchial biopsy: occasionally useful in sarcoid

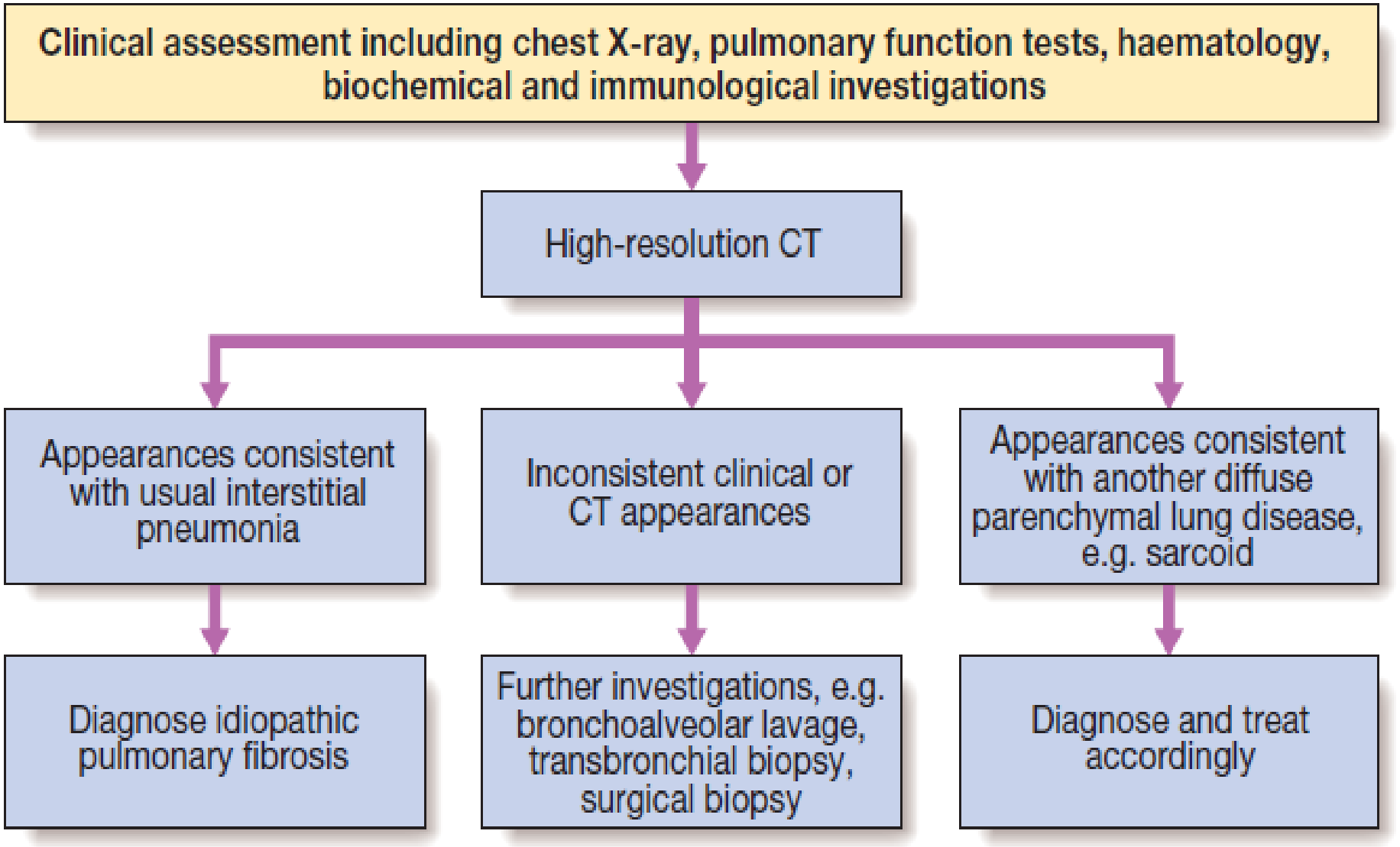
Video-assisted thorascopic lung biopsy (in selected cases)

- Allows pathological classification: presence of asbestos bodies may suggest asbestosis, silica in occupational fibrosing lung disease

Others

- Liver biopsy: may be useful in sarcoidosis
- Urinary calcium excretion: may be useful in sarcoidosis

Assessment


Clinical assessment including chest X-ray, pulmonary function tests, haematology, biochemical and immunological investigations
High-resolution CT
Appearances consistent with usual interstitial pneumonia
Inconsistent clinical or CT appearances
Appearances consistent with another diffuse parenchymal lung disease, e.g. sarcoid
Diagnose idiopathic pulmonary fibrosis
Further investigations, e.g. bronchoalveolar lavage, transbronchial biopsy, surgical biopsy
Diagnose and treat accordingly

When ILD should be suspected

- Progressive SOB or dry cough
- Subacute or chronic onset
- Exposure to respiratory risk factors
- Presence of rheumatological symptoms
- Finger clubbing
- Bilateral crepitations or crackles
- Bilateral infiltrates in radiology
- Restrictive lung diseases in PFT

Conditions that mimic diffuse parenchymal lung disease

Infection

- Viral pneumonia
- *Pneumocystis jirovecii*
- *Mycoplasma pneumoniae*
- Tuberculosis
- Parasite, e.g. filariasis
- Fungal infection

Malignancy

- Leukaemia and lymphoma
- Lymphatic carcinomatosis
- Multiple metastases
- Bronchoalveolar carcinoma

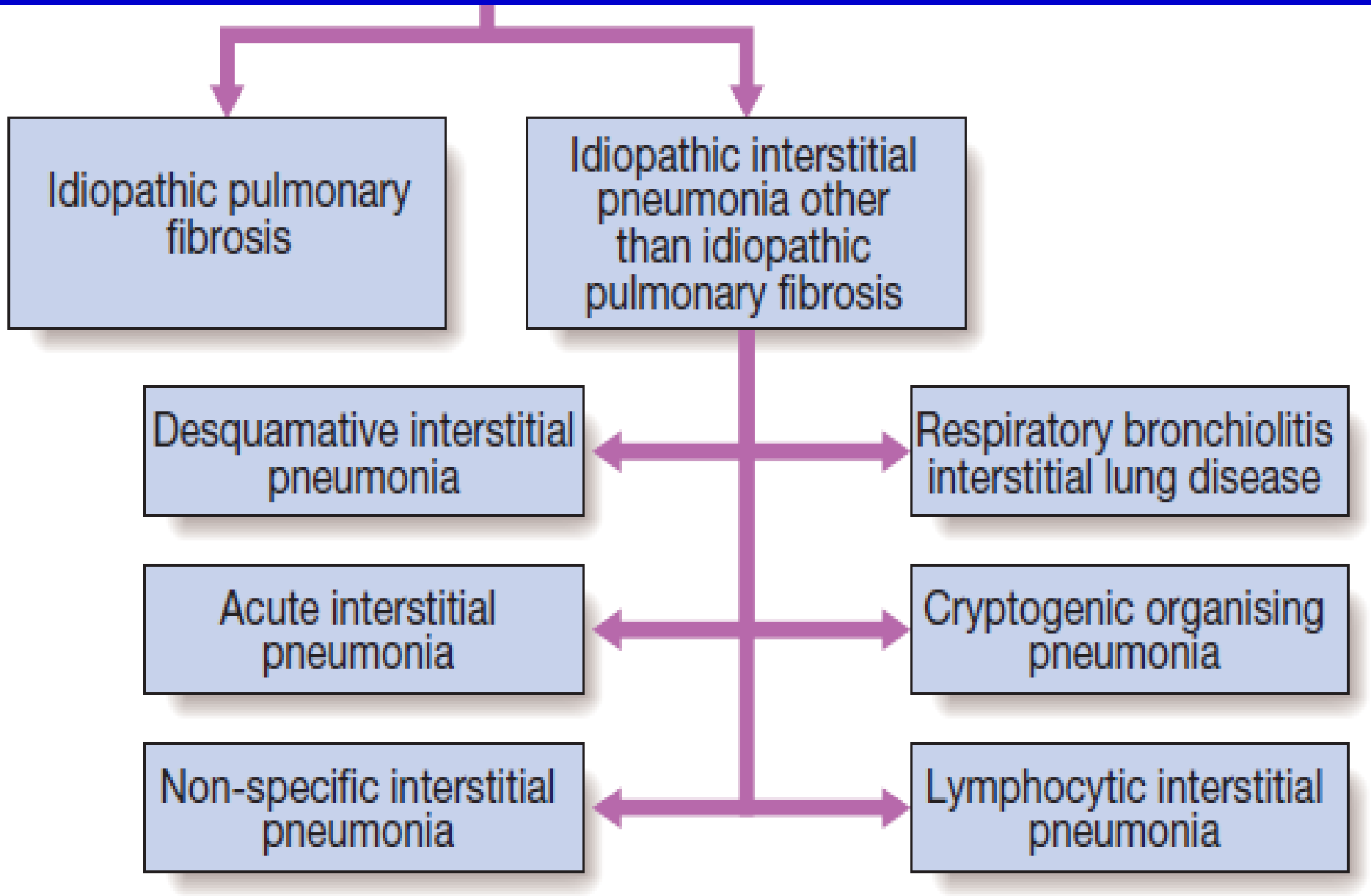
Pulmonary oedema

Aspiration pneumonitis

Idiopathic interstitial pneumonias

- The idiopathic interstitial pneumonias represent a major subgroup of DPLD that are grouped together as a result of their unknown aetiology .
- They are often distinguished by the predominant histological pattern on tissue biopsy; hence they are frequently referred to by their pathological description, e.g. usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia (NSIP). The most important of these is idiopathic pulmonary fibrosis

Idiopathic interstitial pneumonias



Idiopathic pulmonary fibrosis

- Idiopathic pulmonary fibrosis is defined as progressive fibrosing interstitial pneumonia of unknown cause, occurring in adults and associated with the histological or radiological pattern of UIP
- IPF is the most common form of idiopathic interstitial pneumonia
- Typically PTs are between 50-70 years of age
- Etiology
- Unknown suggested association with exposure to viruses (e.g.Epstein–Barr virus), occupational dusts (metal or wood), drugs (antidepressants) or chronic gastro-oesophageal reflux,smoking ,genetics .

Clinical features

History

- more typically presents with progressive breathlessness (which may have been insidious) more obvious with exertion and a non-productive cough.
- History will reveal no etiology of fibrosis
- Constitutional symptoms are unusual.

Examination

- General
- Clubbing in 50% ,cyanosis
- LL oedema in case of core pulmonale
- Local examination
- Decrease expansion bilateral in lower parts, decrease tactile fremitus ,impaired percussion note bilateral basally
- Decrease air entry bilateral basally
- Bi-basal fine late inspiratory crackles of Velcro is characteristic
- 5C (chronic ,dry cough ,cyanosis ,clubbing,crackles)

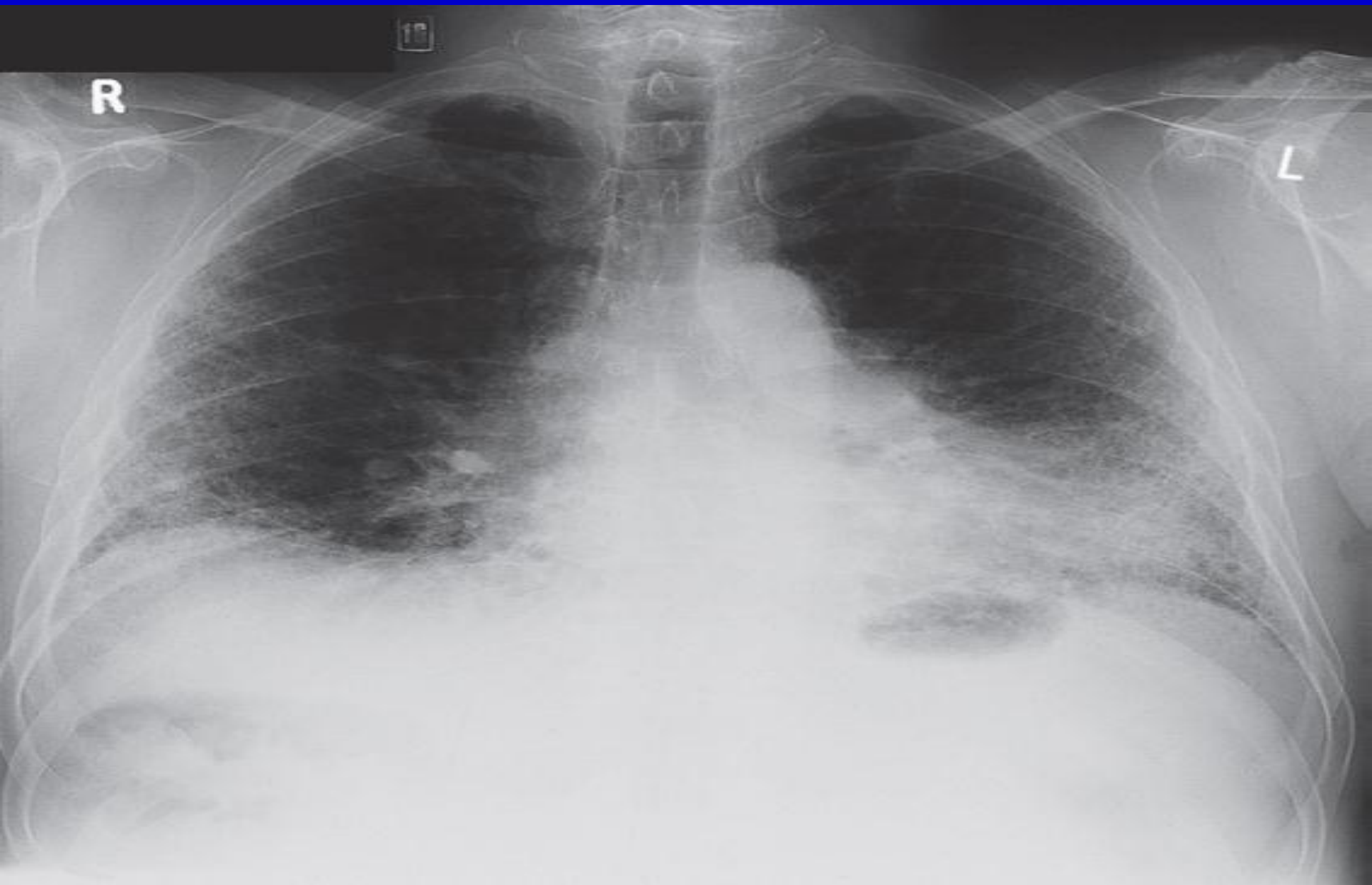
Investigations

- Serological testing
- routinely testing for CRP (C-reactiveprotein), erythrocyte sedimentationrate, antinuclear antibodies (byimmunofluorescence), rheumatoid factor,myositis panel, and anti–cyclic citrullinated peptide.
- Other detailed tests are performed on a case-by-case basis according to associated symptoms and signs
- Radiology
- CXR
- bilateral lower lobe and subpleural reticular shadowing
- The chest X-ray may be normal in individuals with early or limited disease.

Investigations

- HRCT
- The best imaging method in all PTs
- HRCT lung scans typically show patchy,predominantly basilar, subpleural reticular opacities, often associated with traction bronchiectasis and honeycombing(UIP pattern).
- HRCT appearances may also be sufficiently characteristic to suggest an alternative diagnosis

Radiology



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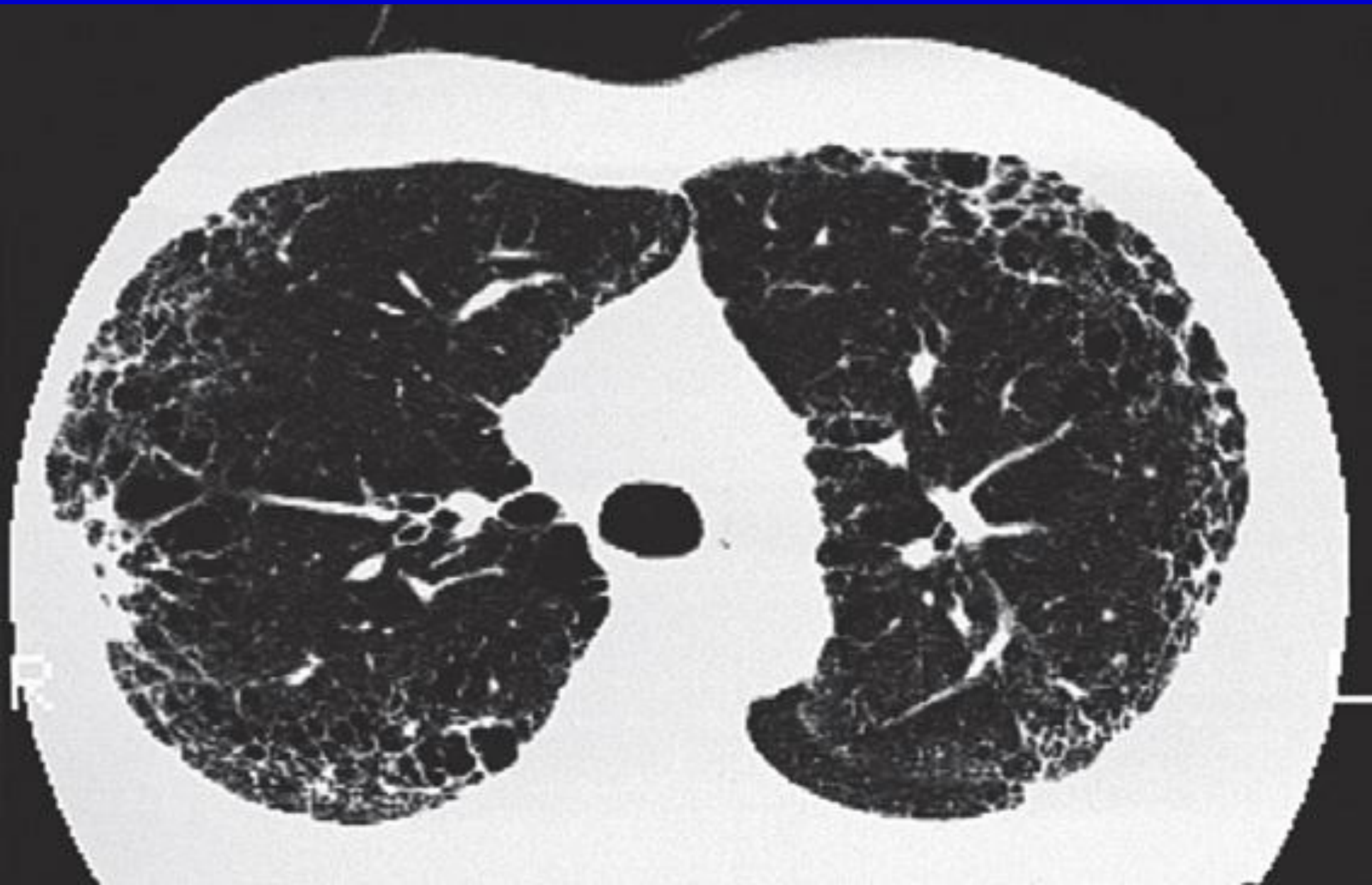

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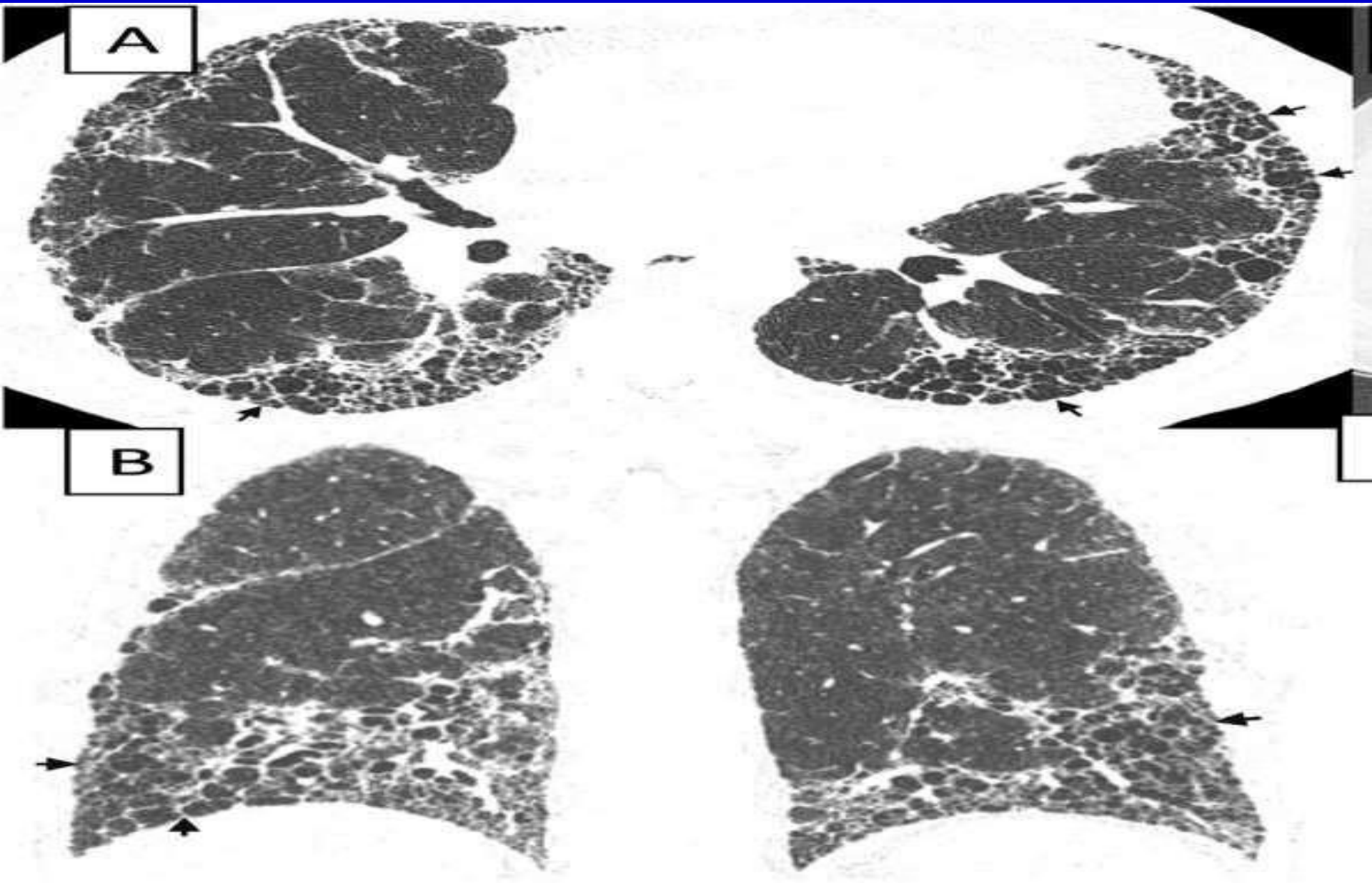


Investigations

- Pulmonary function tests
- classically show a restrictive defect with reduced lung volumes and gas transfer.
- ABG
- Exercise tolerance and demonstrate exercise-induced arterial hypoxaemia.
- Other tests
- These reserved for there is serious consideration of differential diagnoses(atypical findings in HRCT) or susp of infection or a malignant process.
- Bronchoscopy and BAL
- Surgical lung biopsy (UIP is the histological pattern)

Diagnostic Criteria for IPF

- Diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, CTD, drug toxicity), and either #2 or #3:

2. The presence of the HRCT pattern of UIP

3. Specific combinations of HRCT patterns and histopathology patterns in patients subjected to lung tissue sampling.

complications or comorbidities associated with IPF?

- Pulmonary hypertension
- Lung cancer
- Coronary artery disease
- Pulmonary embolism
- Respiratory failure

management

- General treatment
- Control gastro-oesophageal reflux may improve the cough
- Smokers should be advised to stop.
- Influenza and pneumococcal vaccination
- Patients should be encouraged exercise
- Pulmonary rehabilitation
- Domiciliary oxygen should be considered for palliation of breathlessness in severe cases.
- Gastroesophageal reflux (GER) therapy

management

- Specific treatment
- pirfenidone (an antifibrotic agent) or
- nintedanib (a tyrosine kinase inhibitor).
- Other treatments of little benefits
- Immunosuppressive therapy
- Steroids
- some suggest that all patients should receive a course of oral steroids if no contraindications exist (prednisolone40mg OD for 6 weeks) If the response is good, then continue. Optimal duration of therapy is not known .. But treatment for 1-2 years is suggested

management

- azathiopririe, methotrexate, or cyclophosphamide may be used.
- **Anti-fibrotic therapy .**
- Colchicine and D-penicillamine
- Lung transplant

❖ treatment for acute exacerbations

- Treatment is largely supportive.
- Broad-spectrum antibiotics,oxygen supplements, glucocorticoids and and may immunosuppression
- Prognosis
- A median survival of 3-5 years is widely quoted.

Non-specific interstitial pneumonia

- The condition may present as an isolated idiopathic pulmonary condition, but an NSIP pattern is often associated with connective tissue disease, certain drugs, chronic hypersensitivity pneumonitis or HIV infection and care must be taken to exclude these possibilities.
- Presentation similar to that of IPF but usually at a younger age, most commonly in women who have never smoked. It is often associated with a febrile
- illness. HRCT shows bilateral, subpleural ground-glass opacities, often associated with lower lobe volume loss ,, but honeycombing is unusual.
- The prognosis is significantly better than that of IPF,

CRYPTOGENIC ORGANIZING PNEUMONIA

- COP is a clinicopathologic syndrome of unknown etiology.
- Pattern may associated with drugs ,autoimmune diseases,radiation,acute infection
- The onset is usually in the fifth and sixth decades.
- The presentation may be of a flulike illness with cough, fever, malaise,fatigue, and weight loss for 6-8 wks .. Finger clubbing absent
- often misdiagnosed as pneumonia
- markedly raised ESR is common
- Inspiratory crackles are frequently present on examination.

CRYPTOGENIC ORGANIZING PNEUMONIA

- Pulmonary function is usually impaired, with a restrictive defect and arterial hypoxemia being most common
- HRCT
- shows areas of air-space consolidation, ground-glass opacities, small nodular opacities, and bronchial wall thickening and dilation. These changes occur more frequently in the periphery of the lung and in the lower lung zone.
- Treatment
- Glucocorticoid therapy induces clinical recovery in two thirds of patients.

Acute interstitial pneumonia

- Age >40 years
- Often preceded by viral upper respiratory tract infection
- Fever, cough, and dyspnea are common manifestations at presentation.
- AIP is similar in presentation to the acute respiratory distress syndrome (ARDS)
- High mortality rate (>60%)
- HRCT scans show bilateral, patchy, symmetric areas of ground-glass attenuation. Bilateral areas of air-space consolidation
- Histological features **:diffuse alveolar damage**

Desquamative interstitial pneumonia (DIP)

- More common in men and smokers.
- Presents at age 40–60 years.
- Insidious onset of dyspnoea.
- Clubbing in 50%.
- HRCT scans usually show diffuse hazy opacities.
- Biopsy shows increased macrophages in alveolar space, septal thickening and type II pneumocyte hyperplasia.
- Prognosis generally good

OTHERS

- Respiratory bronchiolitis–interstitial lung disease
- is considered to be a subset of DIP
- More common in men and smokers.
- Usually presents at age 40–60 years
- The clinical presentation is similar to that of DIP.
- Lymphocytic interstitial pneumonia (LIP)
- This rare form of ILD occurs in female adults
- slow onset over years
- some of whom have an autoimmune disease or dysproteinemia.
- It has been reported in patients with Sjogren syndrome and HIV infection.

Sarcoidosis

Definition and epidemiology

- Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology that is characterised by the presence of non-caseating granulomas.
- Age : 20-40 yrs
- Sex :female , bimodal
- 16 times more common in blacks
- more frequently described in colder parts of northern Europe. It also appears to be more common and more severe in those from a West Indian or Asian background.
- Sarcoidosis occurs less frequently in smokers

*pathogenesis

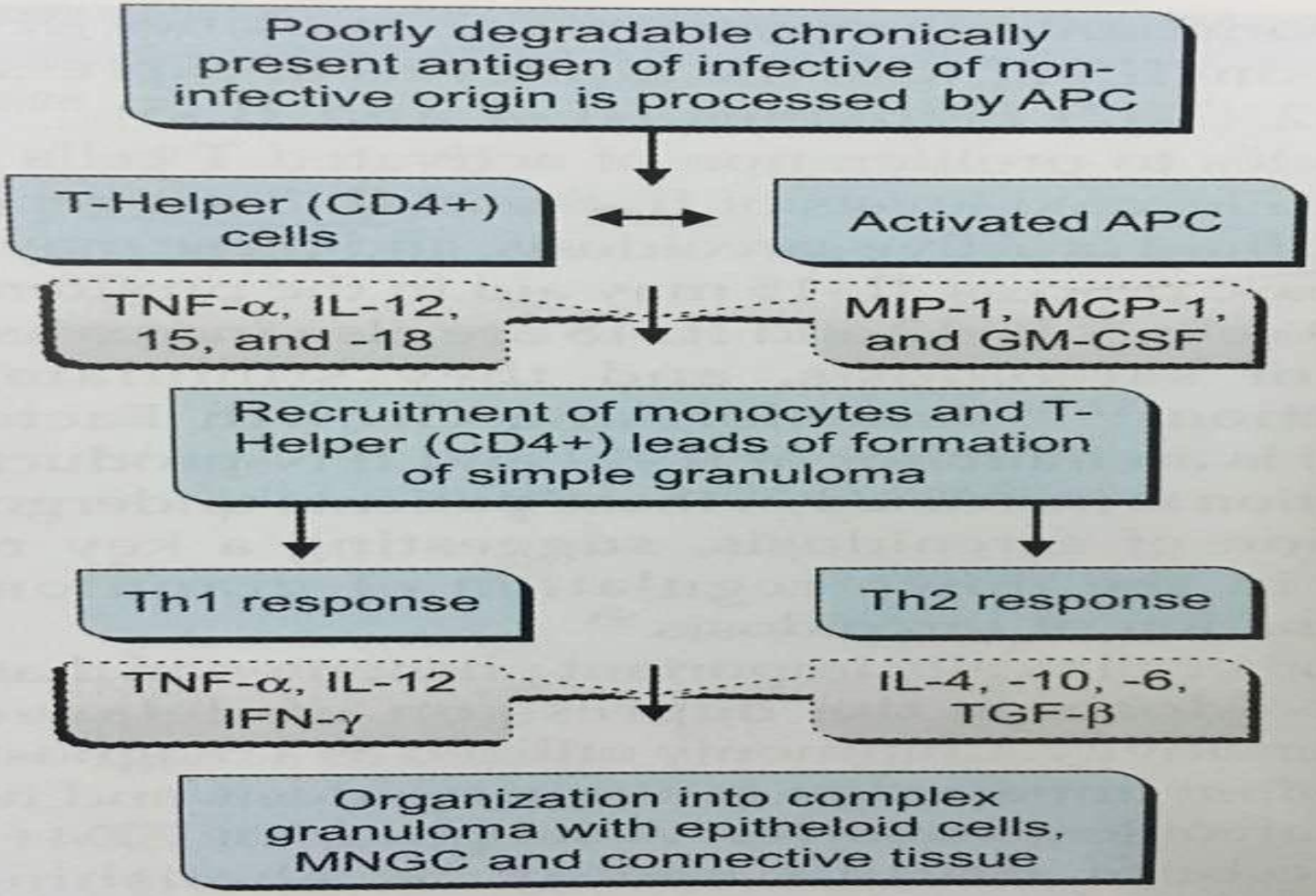
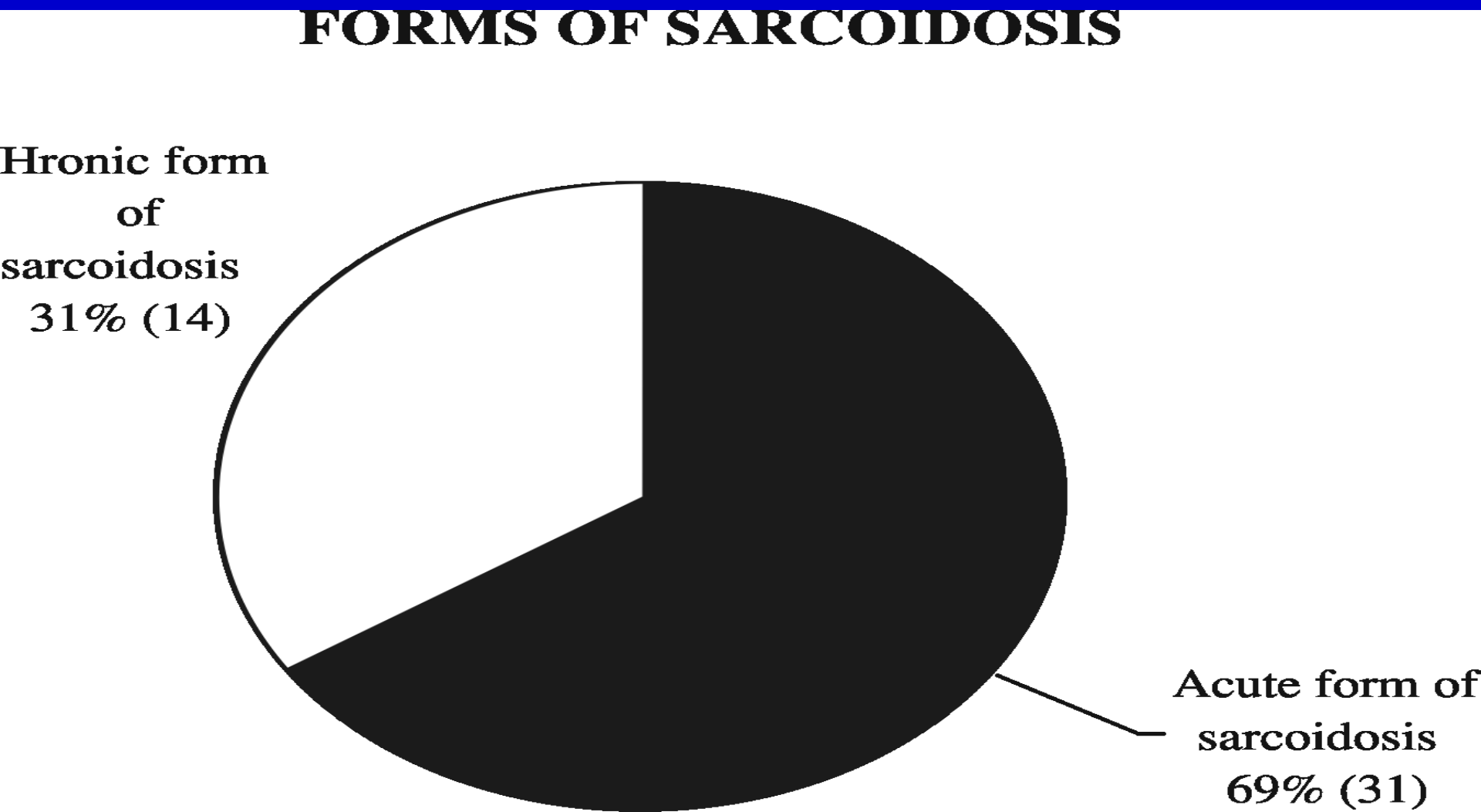
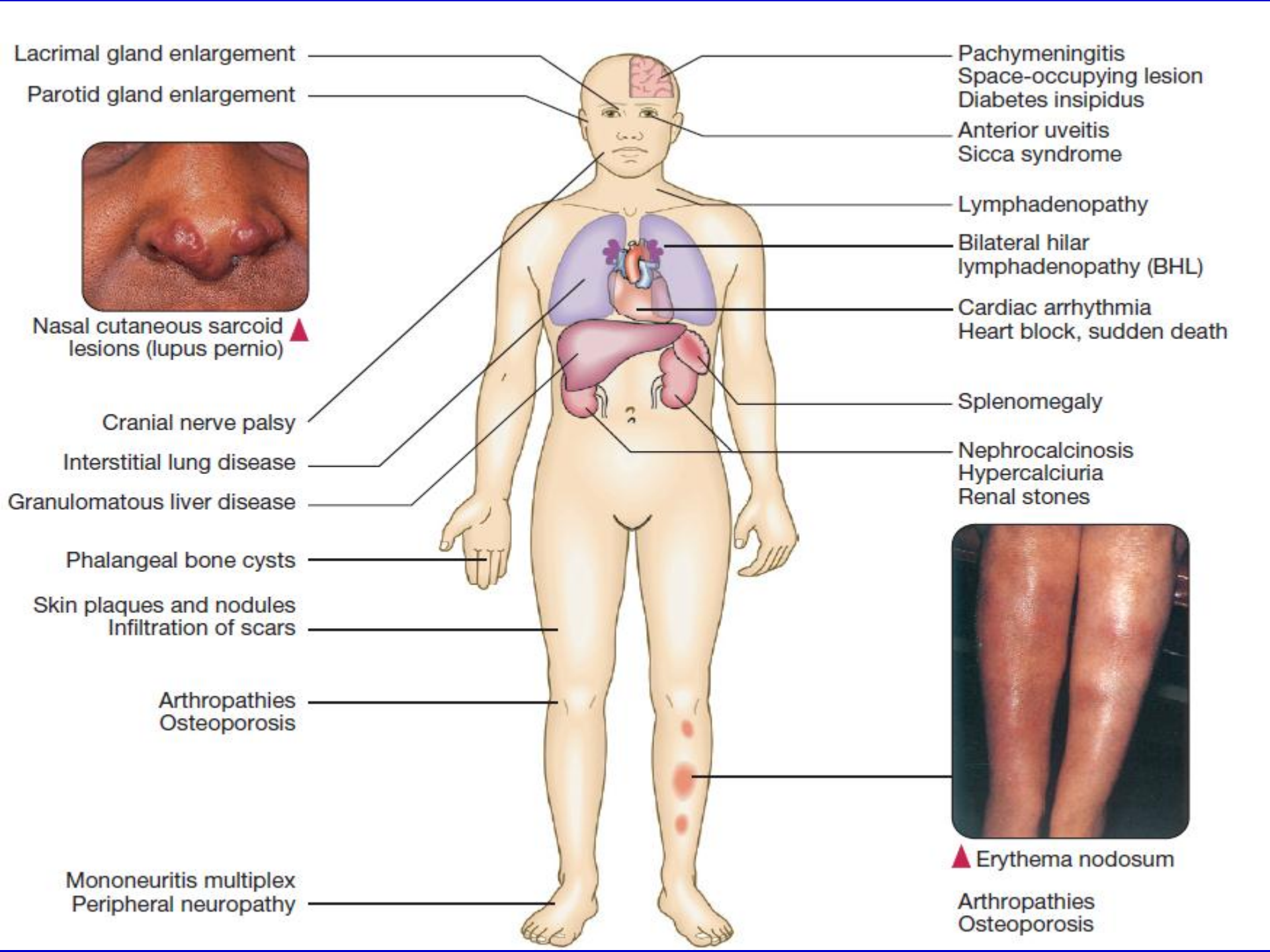


Fig. 96.2: Hypothesis of the development of granulomatous inflammation in sarcoidosis

Clinical features

- Acute versus chronic form




Lacrimal gland enlargement
Parotid gland enlargement
Nasal cutaneous sarcoid lesions (lupus pernio)
Cranial nerve palsy
Interstitial lung disease
Granulomatous liver disease
Phalangeal bone cysts
Skin plaques and nodules
Infiltration of scars
Arthropathies
Osteoporosis
Mononeuritis multiplex
Peripheral neuropathy
Pachymeningitis
Space-occupying lesion
Diabetes insipidus
Anterior uveitis
Sicca syndrome
Lymphadenopathy
Bilateral hilar lymphadenopathy (BHL)
Cardiac arrhythmia
Heart block, sudden death
Splenomegaly
Nephrocalcinosis
Hypercalciuria
Renal stones
Erythema nodosum
Arthropathies
Osteoporosis

Presentation of sarcoidosis

- Asymptomatic: abnormal routine chest X-ray (~30%) or abnormal liver function tests
- Respiratory and constitutional symptoms (20–30%)
- Erythema nodosum and arthralgia (20–30%)
- Ocular symptoms (5–10%)
- Skin sarcoid (including lupus pernio) (5%)
- Superficial lymphadenopathy (5%)
- Other (1%), e.g. hypercalcaemia, diabetes insipidus, cranial nerve palsies, cardiac arrhythmias, nephrocalcinosis

Acute Sarcoidosis

- Löfgren's syndrome -
- acute erythema nodosum with bilateral hilar lymphadenopathy, fever, and polyarthritis, non granulomatous uveitis

- Symptoms are typically abrupt in onset and have a transient course.

- A vesicular or maculopapular rash, acute iritis, conjunctivitis, and Bell's palsy may also be features of acute disease

Pulmonary disease

- Ist and most common involved system (90%)
- up to 50% patients asymptomatic, BHL may be detected in an otherwise asymptomatic individual undergoing a chest X-ray for other purposes
- Pulmonary disease may also present in a more insidious manner with dry cough representing most common presentation , exertional breathlessness also seen .
- Other less common presentation include Chest pain, ,Wheezing,Productive cough- traction bronchiectasis Hemoptysis- bronchiectasis or aspergilloma.
- Pleural disease isuncommon and finger clubbing is not a feature

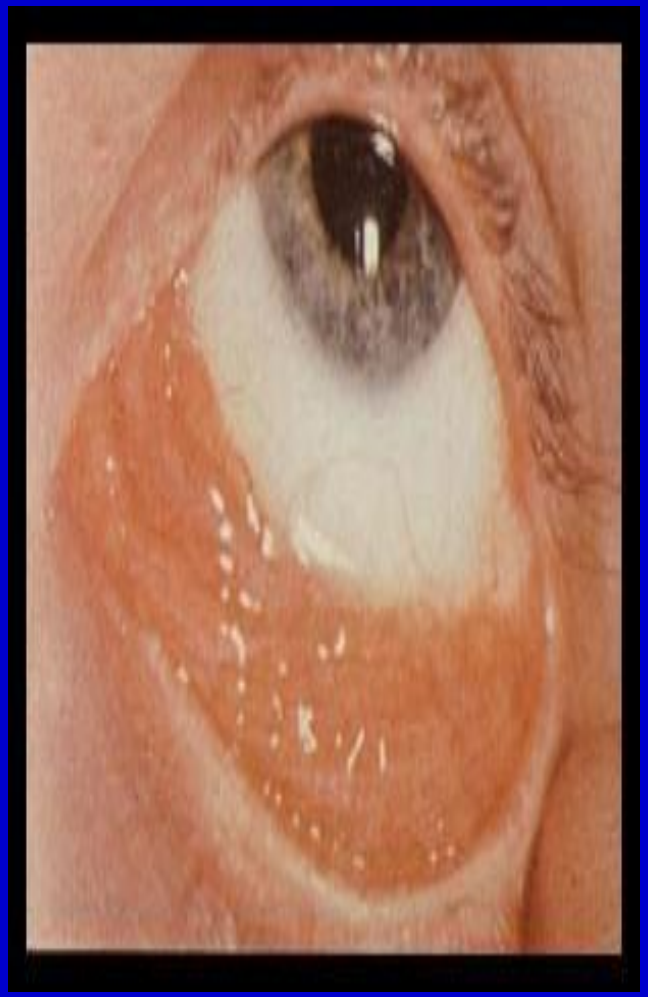
Extrapulmonary Sarcoidosis

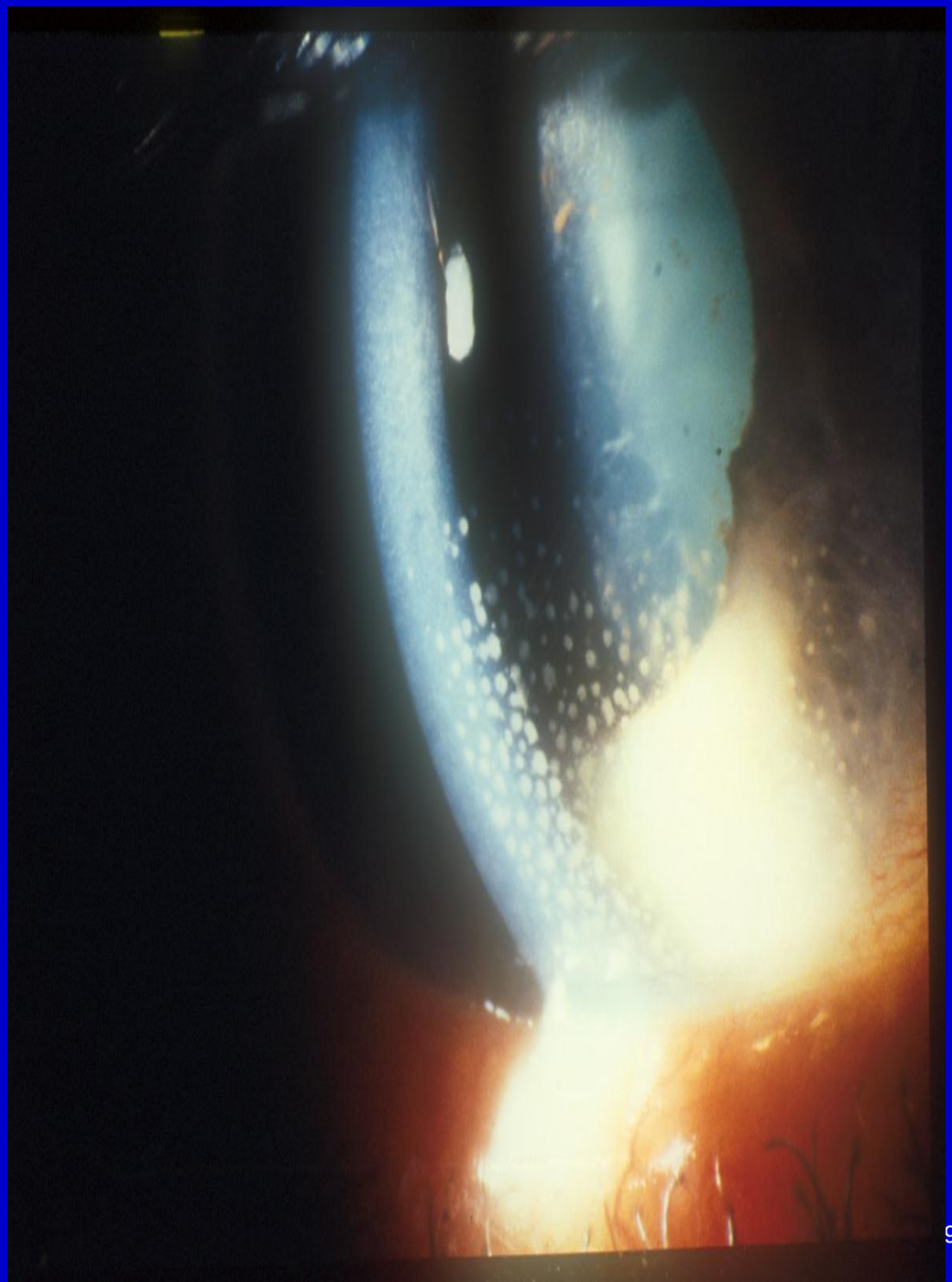
- Upper respiratory tract
- Uncommon up to 20% but disabling.
- Nasal mucosa- crusting,obstruction, discharge. The mucosa erythematous and granular with polypoid hypertrophy.
- Laryngeal and pharyngeal mucosa- hoarseness, cough,dysphagia,dypsnoea
- Patients with sarcoidosis of upper respiratory tract have 50% chance of developing lupus pernio
- Nasal septal and palatal perforations in untreated cases.
- d/d tuberculosis, wegeners granulomatosis, leprosy

Eyes

- upto 25% of sarcoidosis patients and uveitis most common manifestation.
- Anterior uveitis - acutely, with pain, photophobia, lacrimation, and redness, self limiting
- Posterior uveitis is typically gradual in onset and is more likely to result in visual morbidity, chronic form of disease.
- Chronic uveitis leads to glaucoma, cataracts and blindness ,Keratoconjunctivitis sicca
- Papilledema
- 10% of patients with sarcoid-associated uveitis develop blindness in at least one eye.

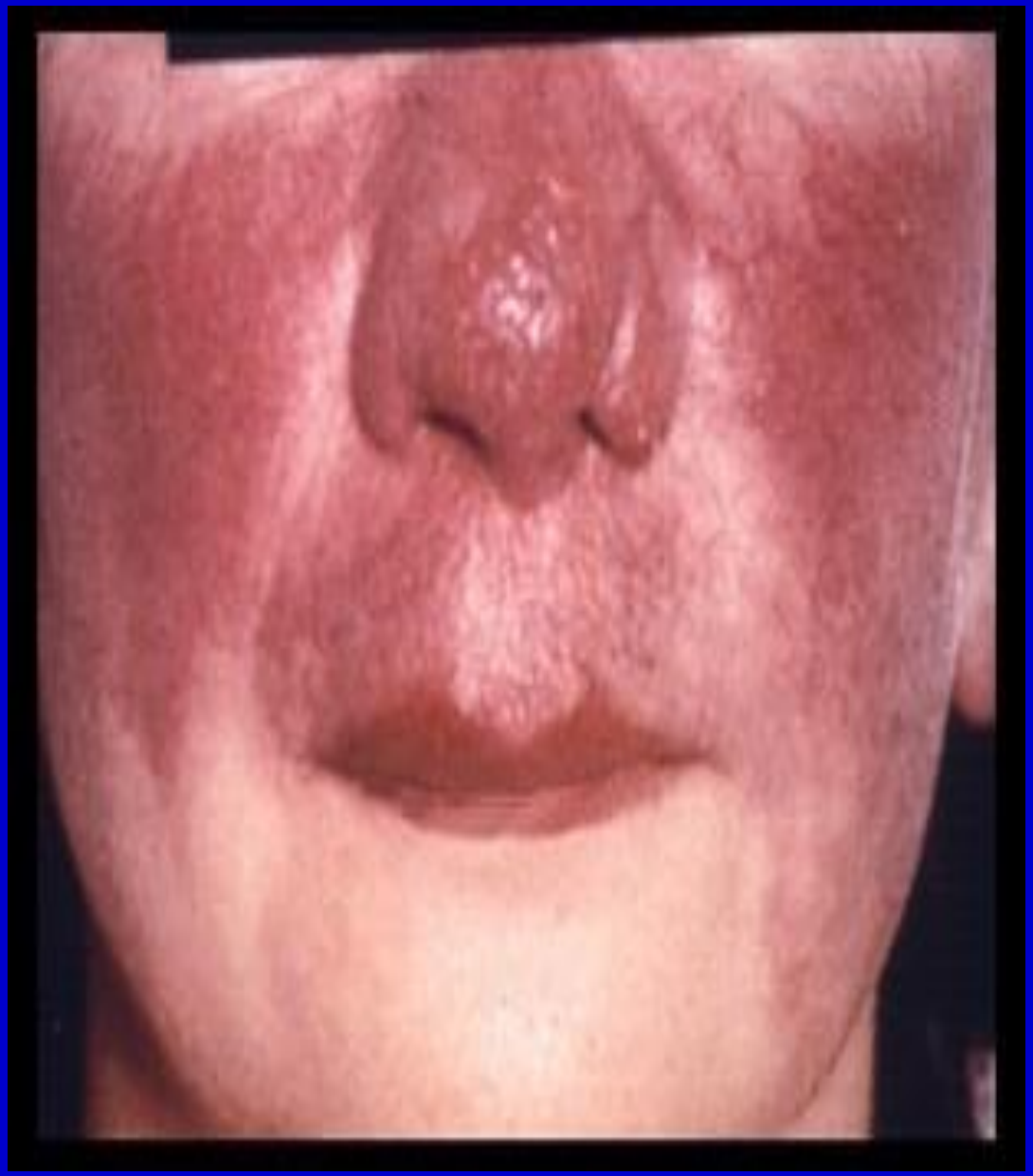
Conguctivitis





Skin

- In 25% of PTs
- Most common manifestation- erythema nodosum.
- Erythema nodosum typically presents as raised, tender, red nodules, 1 to 2 cm in diameter, on the anterior surface of the lower legs.
- lupus pernio is a rare lesion,most severe dermatological manifesation - purplish plaques typically found over the nose, cheeks, lips, and ears. Associated with poor prognosis and severe pulmonary disease.
- skin abnormalities include red-brown to orange macules and papules, keloids, and hyper- or hypopigmentation



Extrapulmonary Sarcoidosis

- Lymphatic system
- hilar and mediastinal lymph nodes (>90% of patients);
- peripheral lymphadenopathy (5%–30%).
- cervical, axillary, epitrochlear, and inguinal regions.
  - nontender, mobile
- Liver
- have hepatomegaly or biochemical evidence of disease
- Symptoms usually absent
- Cholestasis, fibrosis, cirrhosis, portal hypertension, and the Budd-Chiari syndrome have been seen

Nervous System

- Peripheral neuropathy or mononeuritis multiplex
- Cranial nerve palsy- 7th nerve facial palsy is most common (sarcoidosis is most common cause of bilateral facial nerve palsy)
- Acute, transient, and can be unilateral or bilateral
- HEERFORDT'S SYNDROME: facial palsy accompanied by fever, uveitis, and enlargement of the parotid gland.
- Lymphocytic meningitis Meningoencephalitis ,deafness
- Epilepsy
- Brain stem and spinal cord syndromes

Extrapulmonary Sarcoidosis

- Hematopoietic system: splenomegaly common
- Genitourinary system:
- nephrocalcinosis due to unexplained increase in senstivity to vitamin D leading to increased absorption of calcium from gut.
- Rarely glomerulonephritis and sarcoidosis of epididymis

- Involvement of myocardium leading to dysrhythmias,conduction disorders,pericarditis, heart failure, restrictive cardiomyopathy and sudden death

- Musculoskeletal
- Acute :polyarthritis
- Chronic oligoarthritis ,ankle involvement
- Bone involvement most commonly affects terminal phalanges of hands and feet and proximal bones in severe cases.
- Complications
- such as bronchiectasis, aspergilloma, pneumothorax, pulmonary hypertension and cor pulmonale have been reported but are rare.

Investigations

- Cbc :lymphopenia
- LFT; may be mildly deranged.
- Electrolytes :hypercalcaemia in 5%
- Urine Hypercalciuria 20%
- Serum ACE levels
  - Elevated in 30-80 of cases
  - Neither sensitive nore specific
  - Elevated levels are seen in infections ,graulomatous disease, lymphoma, hepatitis, DM, thyroid disease. Thus SACEis not recommended as a diagnostic test
  - Provides good monitor of disease activity

- Kveim-stiltzbach test :
  - Intradermal injection of homogenised tissue of organs involved with sarcoidosis causes delayed cutaneous reaction in 4 – 6weeks.
- PPDskin test.
  - More than 70% negative
- pulmonary function testing may show a restrictive defect or combined (restrictive and obstructive) accompanied by impaired gas exchange.
- Exercise tests may reveal oxygen desaturation.

Radiology

- Chest radiograph
- abnormal in 90% of sarcoidosis patients.
- Bilateral hilar lymphadenopathy in 50-85%cases.
- Lymph nodes big and sharply defined with clear line of transluscency between mediastinum and lymph nodes- **POTATO NODES**.
- Unilateral lymphadenopathy- rare Pulmonary infiltrates in 25-60% cases

Chest X-ray changes in sarcoidosis

Stage I: BHL (usually symmetrical); paratracheal nodes often enlarged

- Often asymptomatic, but may be associated with erythema nodosum and arthralgia. The majority of cases resolve spontaneously within 1 yr

Stage II: BHL and parenchymal infiltrates

- Patients may present with breathlessness or cough. The majority of cases resolve spontaneously

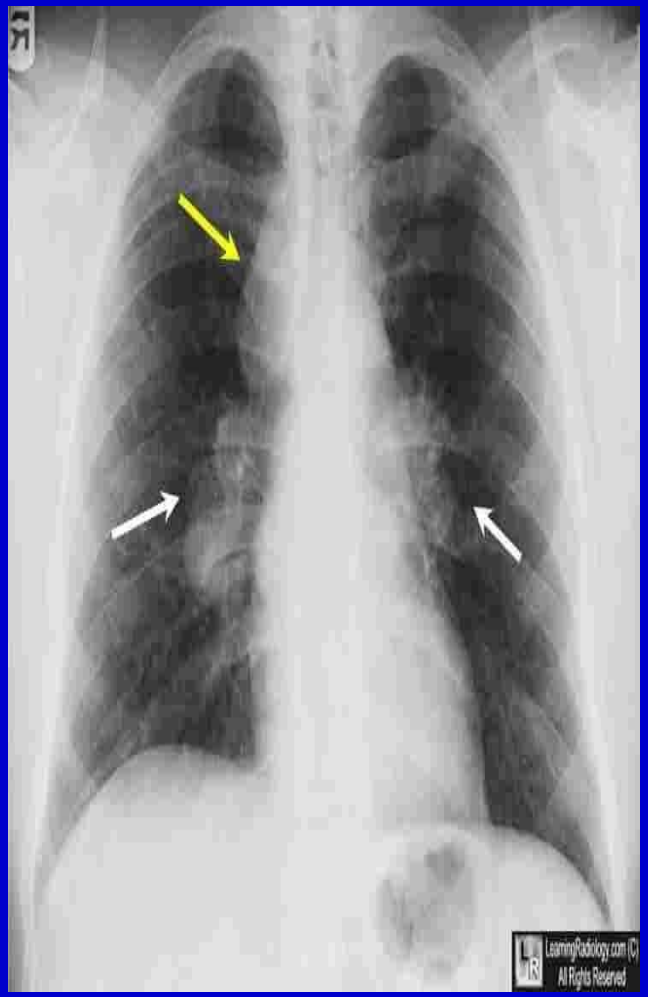
Stage III: parenchymal infiltrates without BHL

- Disease less likely to resolve spontaneously

Stage IV: pulmonary fibrosis

- Can cause progression to ventilatory failure, pulmonary hypertension and cor pulmonale

(BHL = bilateral hilar lymphadenopathy)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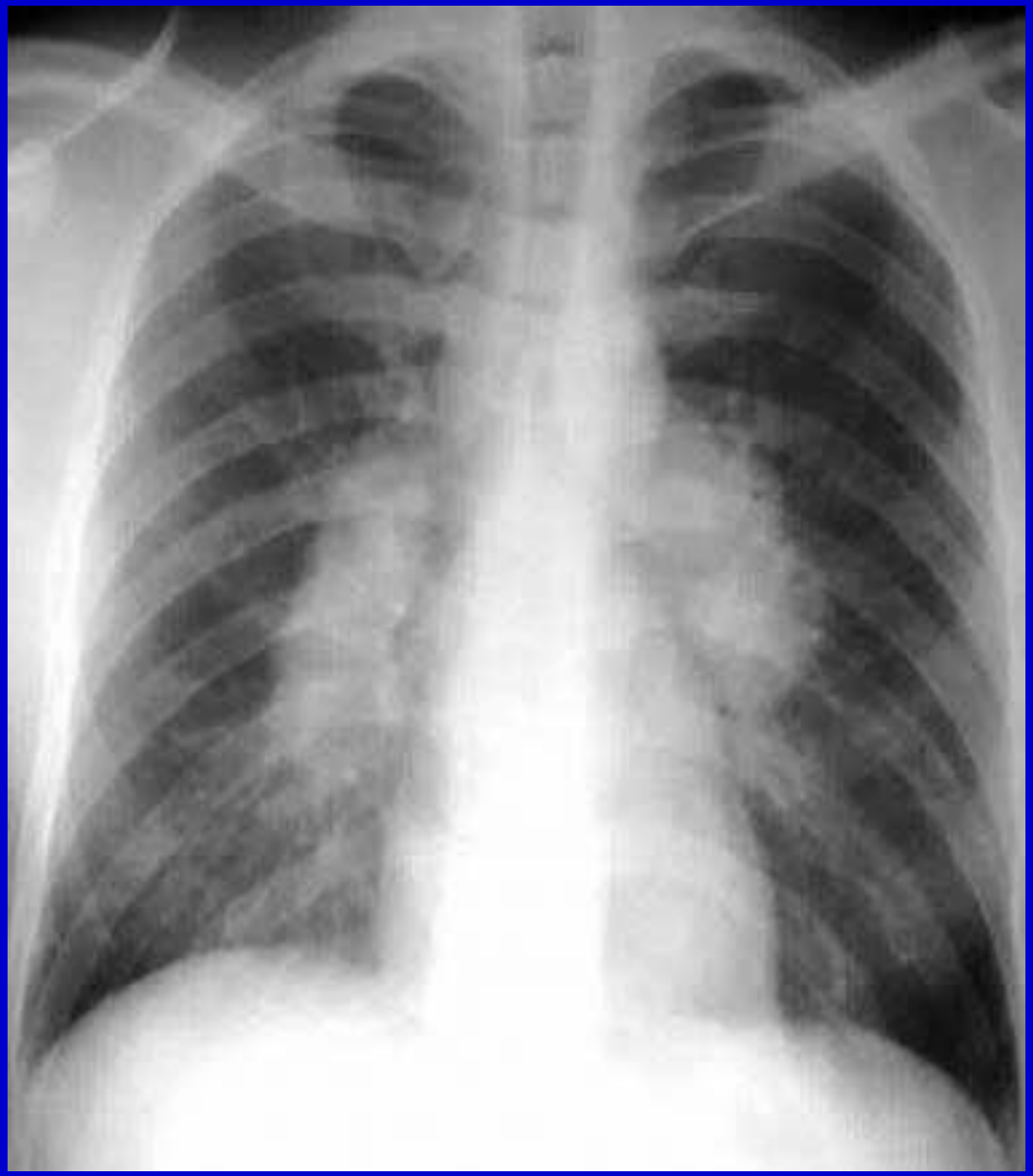
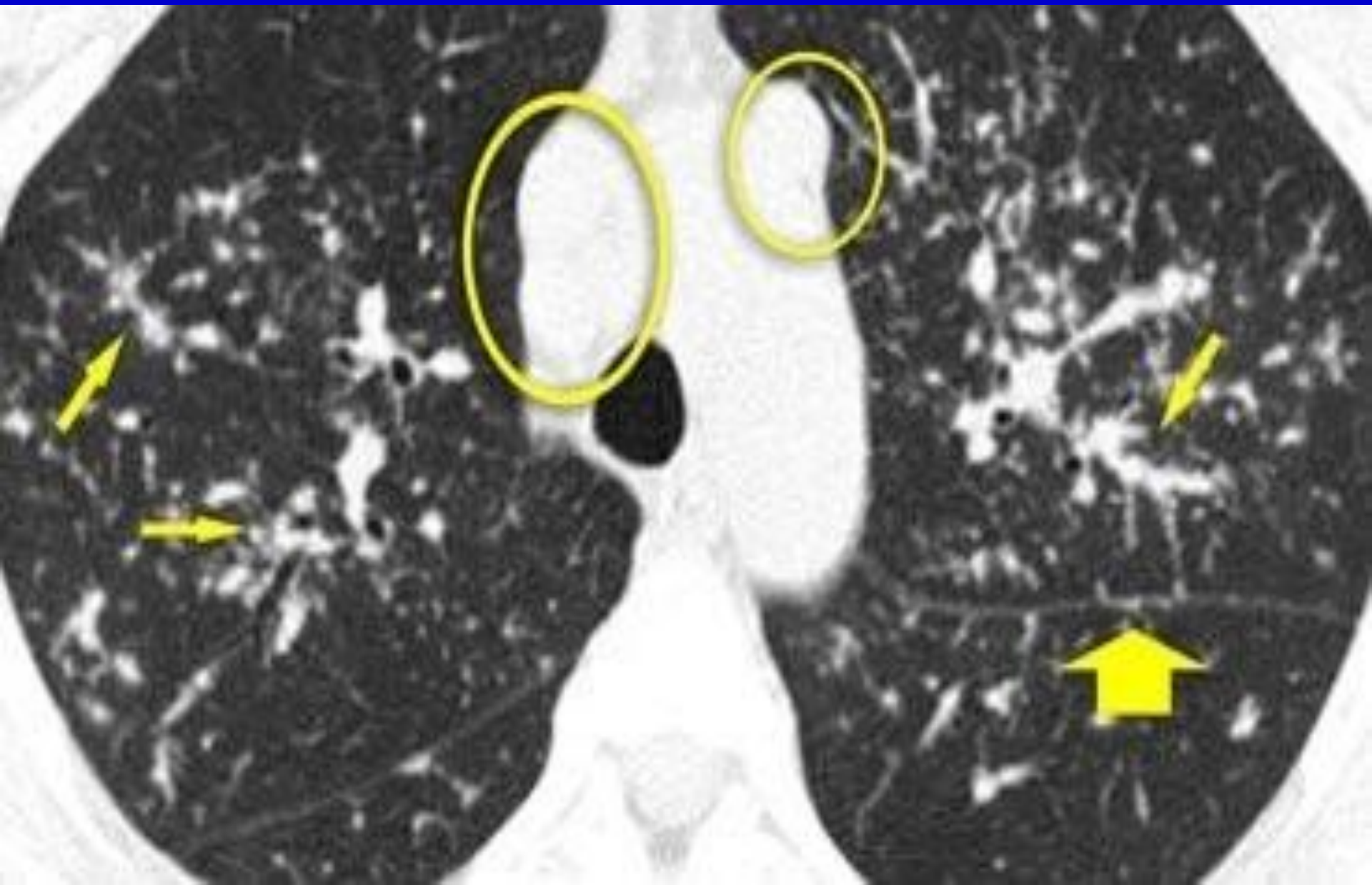


HRCT

- HRCT findings in Sarcoidosis.
- Common findings:
- Small nodules in a perilymphatic distribution (i.e. along subpleural surface and fissures, along interlobular septa and the peribronchovascular bundle).
- Upper and middle zone predominance.
- Lymphadenopathy in left hilus, right hilus and paratracheal (1-2-3 sign). Often with calcifications



Radiology

- Gallium 67 scan
- Increase uptake in sarcoidosis
- Not specific for sarcoidosis.
- Expensive and radiation exposure
- PET scanning can detect extrapulmonary disease.

Investigations

- Tissue biopsy is essential.
- Biopsy almost always +ve if skin, lymphnodes, conjunctiva involved, accessible sites.
- Transbronchial lung biopsy is usually performed because high yield and relative safe.
- Combining EBUS with TBNA increases the sensitivity
- Bronchoalveolar lavage fluid typically contains an increased CD4:CD8 T-cell ratio

Others

Mediastionscopy or VATS or open lung biopsy increase yield .

Others tests according to organ involved

- Cardiac
- ECG
- Holter monitoring
- Thalium or sestamibi myocardial scan Cardiac MRI
- Cardiac PET
- Neurology
- Brain or spine MRI with gadolinium enhancement

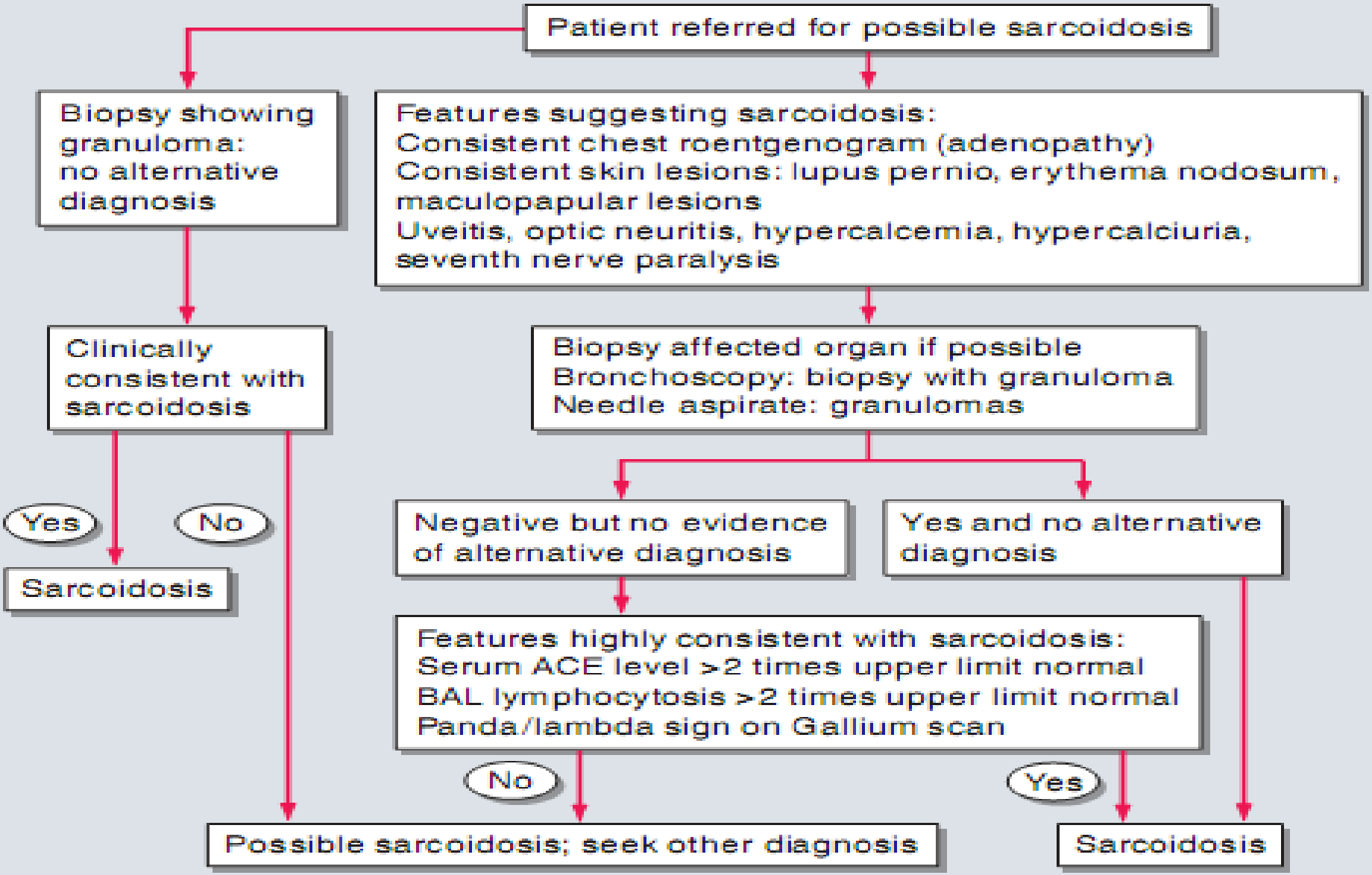
CSF examination

- EMG or nerve conduction studies

ATS criteria diagnosis of pulmonary sarcoidosis

- presence of a consistent clinical and radiographic picture
- demonstration of noncaseating granulomas on biopsy
- exclusion of other conditions that can produce granulomatous inflammation

Diagnosis


Patient referred for possible sarcoidosis
Biopsy showing granuloma: no alternative diagnosis
Features suggesting sarcoidosis:
Consistent chest roentgenogram (adenopathy)
Consistent skin lesions: lupus pernio, erythema nodosum, maculopapular lesions
Uveitis, optic neuritis, hypercalcemia, hypercalciuria, seventh nerve paralysis
Clinically consistent with sarcoidosis
Biopsy affected organ if possible
Bronchoscopy: biopsy with granuloma
Needle aspirate: granulomas
Yes
No
Sarcoidosis
Negative but no evidence of alternative diagnosis
Yes and no alternative diagnosis
Features highly consistent with sarcoidosis:
Serum ACE level >2 times upper limit normal
BAL lymphocytosis >2 times upper limit normal
Panda/lambda sign on Gallium scan
No
Yes
Possible sarcoidosis; seek other diagnosis
Sarcoidosis

Diagnosis

- The occurrence of erythema nodosum with BHL on chest X-ray is often sufficient for a confident diagnosis, without recourse to a tissue biopsy.
- Similarly, a typical presentation with classical HRCT
- features may also be accepted.
- In other instances, however, the diagnosis should be confirmed by histological examination of the involved organ.

Management

- Acute illness
- NSAIDS
- Occasionally short course of prednisolone is needed
- Chronic illness
- The majority of patients enjoy spontaneous remission and so, if there is no evidence of organ damage,

systemic glucocorticoid therapy can be withheld for 6 months

- Local steriods may only needed
- Topical glucocorticoids may be useful in cases of mild
- ant uveitis,
- inhaled glucocorticoids may used for cough

Management

- Indications of systemic immunosuppresive
- Pulmonary
- Stage I or stage 11

Only if persistent more than 6 months ,or significant symptoms or constitutional symptoms

- Stage 111,1V
- Extrapulmonary diseases
- hypercalcaemia
- renal impairment ,cardiac involvement
- Uveitis,skin lesions other than erythema nodosum
- Cns involvement ,

Management

- systemic glucocorticoid therapy
- prednisolone (at a starting dose of 20–40 mg) for 4-6wks then tappered to maintanance 7.5-10 mg over 6 months .
- Other immunosuppressive
- methotrexate (10–20 mg/week),
- azathioprine (50–150 mg/day) and
- specific tumour necrosis factor alpha (TNF-α) inhibitors.
- Chloroquine, hydroxychloroquine and low-dose thalidomide may be useful in cutaneous sarcoid with limited pulmonary involvement

Management

- single lung transplantation.
- Prognosis
- The overall mortality is low (1–5%)
- Features suggesting poor prognosis include
  - Age over 40,
  - Afro-Caribbean ethnicity,
  - persistent symptoms for more than 6 months,
  - the involvement of more than three organs,
  - lupus pernio
  - and a stage III/IV chest X-ray.

Respiratory involvement in connective tissue disorders

Introduction

- Pulmonary complications of connective tissue disease are common, affecting the airways, alveoli, pulmonary vasculature, diaphragm and chest wall muscles, and the chest wall itself.
- 15%of patients with an interstitial lung disease have an underlying connective-tissue disease
- In some instances, pulmonary disease may precede the appearance of the connective tissue disorder
- Mechanisim
- Direct (NSIP most common form)
- Indirect (drugs ,secondary infections, esophageal dysfunction and respiratory muscle weakness)

Introduction

Interstitial lung diseases associated with

CTD	Frequency ofILD (%)	Comment
Systemic sclerosis	45clinically significant	More common in diffuse disease; topoisomerase-1 antibodies
Rheumatoid arthritis	20to 30	Increased risk with cigarette smoking
Polymyositis /dermatomyositis	20to 50	More common with anti-synthetase antibodies
Sjögren's syndrome	Up to 25	-
Systemic lupus erythematosus	2to 8	Usually in patientswith multisystem disease
Mixed connective tissue disease	20to 60	–

http://arthritis-12213, 2010Castelino and Varga Arthritis Research &Therapy 12/4/213 research.com/content/

Introduction

Systemic symptoms		CTD
Dermatological	Heliotrope rash, Gattron'spapule, mechanic's hand. history of skin tightness and thickening, telangiectasias, Raynaud's phenomenon, or digital pitting. Malar rash, photosensitivity skin reaction, or hair loss.	Dermatomyositis Systemic sclerosis (scleroderma(SLE
Gastrointestinal	Esophageal motility problems as acid reflux (chest burning or pressure, cough after meals, regurgitation offood(	Systemic sclerosis and polymyositis
Musculoskeletal	Arthralgias,morning stiffness, joint swelling and erythema, and deformities Swollen fingers ("sausage digits("	Rheumatoid arthritis, Sjögren syndrome, or mixed connective tissue disorder. systemic sclerosis and polymyositis
Ophthalmologic	Dry eyes or the use of eye drops may uncover sicca syndrome history of uveitis	Sjögren syndrome SLE or sarcoidosis

Rheumatoid arthritis

- Pulmonary involvement in rheumatoid disease is important, accounting for around 10–20% of the mortality associated with the condition
- The majority of cases occur within 5 years of the rheumatological diagnosis but pulmonary manifestations may precede joint involvement in 10–20%.
- Pleuritis, the most common pulmonary manifestation of RA, may produce pleuritic chest pain and dyspnea, as well as a pleural friction rub and effusion
- Pleural effusion is common, especially in men with seropositive disease. Effusions are usually small and unilateral, but can be large and bilateral.

Rheumatoid arthritis

- Biochemical testing shows an exudate with markedly reduced glucose levels and raised lactate dehydrogenase (LDH).
- ILD in up to 20% of cases
- Rheumatoid pulmonary nodules are usually asymptomatic and detected incidentally on imaging. They are most often multiple and subpleural in site
- The combination of rheumatoid nodules and pneumoconiosis is known as Caplan's syndrome
- Bronchitis and bronchiectasis are both more common in rheumatoid patients
- obliterative bronchiolitis may develop rarely and fatal

Systemic lupus erythematosus

- Lung disease is a common complication in SLE.
- Pleuritis with or without effusion is the most common pulmonary manifestation.
- The most serious manifestation of lupus is an acute alveolitis that may be associated with diffuse alveolar haemorrhage
- Chronic, progressive ILD is uncommon
- ‘shrinking lungs:has been attributed to diaphragmatic myopathy, The chest X-ray show elevated diaphragms
- Other lung manifestations:pulmonary vascular disease, pulmonary hemorrhage, uremic pulmonary edema,infectious and organized pneumonia.

Systemic sclerosis

- Pulmonary involvement is frequent in SSc and is the leading cause of death.
- The two principal forms are ILD and pulmonary vascular diseases.
- Less frequent pulmonary manifestations include aspiration pneumonitis complicating chronic gastroesophageal reflux,pulmonary hemorrhage due to endobronchial telangiectasia, obliterative bronchiolitis, pleural reactions, restrictive ventilatory defect dueto chest wall fibrosis, spontaneous pneumothorax, and drug-induced lung toxicity.
- The incidence of lung cancer is increased

Systemic sclerosis

- Interstitial Lung Disease (ILD)
- Evidence of ILD can be found in up to90% of patients with SSc at autopsy and 85% by thin-section highresolution computed tomography (HRCT).
- Risk factors include male gender, African- American race, diffuse skin involvement
- Pulmonary Arterial Hypertension
- develops in approximately 15% of patients with SSc
- Risk factors for PAH include limited cutaneous disease, older age at disease onset, severe Raynaud's phenomenon

Polymyositis and Dermatomyositis (PM/DM)

- ILD occurs in ~10% of patients with PM/DM
- ILD occurs more commonly in the subgroup of patients with an anti-Jo-1 antibody that is directed to histidyl tRNA synthetase
- Weakness of respiratory muscles contributing to aspirationpneumonia may be present.
- A rapidly progressive illness characterized by diffuse alveolar damage may cause respiratory failure.

Disorder	Airways	Parenchyma	Pleura	Diaphragm and chest wall
Rheumatoid arthritis	Bronchitis, obliterative bronchiolitis, bronchiectasis, crico-arytenoid arthritis, stridor	Pulmonary fibrosis, nodules, upper lobe fibrosis, infections	Pleurisy, effusion, pneumothorax	Poor healing of intercostal drain sites
Systemic lupus erythematosus	–	Pulmonary fibrosis, 'vasculitic' infarcts	Pleurisy, effusion	Diaphragmatic weakness (shrinking lungs)
Systemic sclerosis	Bronchiectasis	Pulmonary fibrosis, aspiration pneumonia	–	Cutaneous thoracic restriction (hidebound chest)
Dermatomyositis/ polymyositis	Bronchial carcinoma	Pulmonary fibrosis	–	Intercostal and diaphragmatic myopathy
Rheumatic fever	–	Pneumonia	Pleurisy, effusion	–

Malar flash in SLE

- Heliotrope rash in woman with dermatomyositis

SSC Finger tips unfarctios

- sclerodactly

The ANCA-associated vasculitides

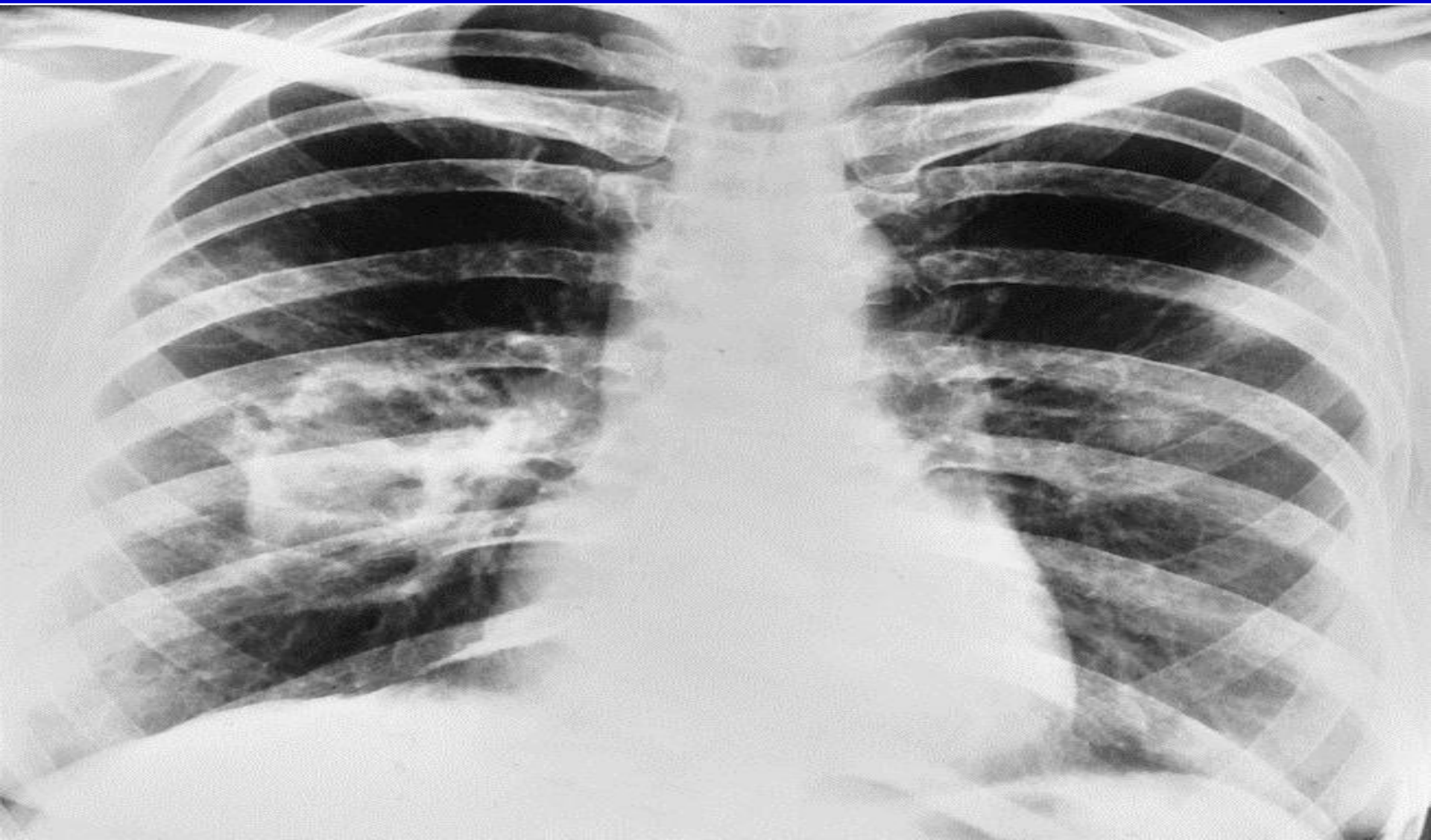
Granulomatosis with polyangiitis

- (formerly referred to as Wegener's granulomatosis) is a rare vasculitic and granulomatous condition
- The lung is commonly involved in systemic forms of the disease
- Involvement of the upper airways occurs in 95% of patients with granulomatosis with polyangiitis (Wegener's). Patients often present with severe upper respiratory tract findings such as paranasal sinus pain and drainage and purulent or bloody nasal discharge, with saddle nose deformity. Serous otitis media occur
- Respiratory symptoms include cough, haemoptysis and chest pain.

Granulomatosis with polyangiitis

- Renal disease (77% of patients) generally dominates the clinical picture
- rapidly progressive renal failure usually ensues unless appropriate treatment is instituted.
- Eye involvement in (52% of patients),
- Skin lesions in (46% of patients)
- Radiological features include multiple nodules and
- cavitation that may resemble primary or metastatic carcinoma,or a pulmonary abscess.
- Tissue biopsy confirms the distinctive pattern of necrotising granulomas and necrotising vasculitis
- positive antiproteinase-3 ANCA.

Granulomatosis with polyangiitis



MICROSCOPIC POLYANGIITIS

- Microscopic polyangiitis and granulomatosis with polyangiitis (Wegener's) share similar clinical features.
- Glomerulonephritis occurs in at least 79% of patients
- and can be rapidly progressive, leading to renal failure.
- Hemoptysis may be the first symptom of alveolar hemorrhage, which occurs in 12% of patients. Other manifestations include mononeuritis multiplex
- and gastrointestinal tract and cutaneous vasculitis.
- Upper airway diseaseand pulmonary nodules are not typically found in microscopic polyangiitis

Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome

- a small-vessel vasculitis
- It is associated with eosinophilia.
- prodromal period for many years, characterised by allergic rhinitis nasal polyposis and late-onset asthma that is often difficult to control.
- The typical acute presentation is with a triad of skin lesions (purpura or nodules),asymmetric mononeuritis multiplex and eosinophilia.
- Pulmonaryi nfiltrates and pleural or pericardial effusions due to serositis may be present.
- Up to 50% of patients have abdominal symptoms provoked by mesenteric vasculitis

Goodpasture's disease

- Pulmonary hemorrhage and glomerulonephritis are features in most patients with this disease. Autoantibodies to renal glomerular and lung alveolar basement membranes are present.
- Pulmonary disease usually precedes renal involvement and includes radiographic infiltrates and hypoxia with or without haemoptysis.
- It occurs more commonly in men and almost exclusively in smokers
- This syndrome can present and recur as DAH without an associated glomerulonephritis.
- diagnosis is by demonstrating linear immunofluorescence in lung tissue.

Pulmonary eosinophilia

Pulmonary eosinophilia

- The term encompasses a group of disorders of different aetiology, characterized by pulmonary infiltrates on imaging along with a increased number of eosinophils in lung tissue, in sputum, in peripheral blood and/or in BAL fluid, with resultant increased respiratory symptoms and the potential for systemic manifestations.
- the first step in classifying pulmonary eosinophilic syndromes is distinguishing between primary pulmonary eosinophilic lung disorders and those with eosinophilia that are secondary to a specific cause such as a drug reaction, an infection, a malignancy, or another pulmonary condition such as asthma

Pulmonary Infiltrates with Eosinophilia

Primary Pulmonary Eosinophilic Disorders
Acute eosinophilic pneumonia
Chronic eosinophilic pneumonia
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Hypereosinophilic syndrome
Pulmonary Disorders of Known Cause Associated with Eosinophilia
Asthma and eosinophilic bronchitis
Allergic bronchopulmonary aspergillosis
Bronchocentric granulomatosis
Drug/toxin reaction
Infection (Table 310-4)
Parasitic/helminthic disease
Nonparasitic infection
Lung Diseases Associated with Eosinophilia
Cryptogenic organizing pneumonia
Hypersensitivity pneumonitis
Idiopathic pulmonary fibrosis
Pulmonary Langerhans cell granulomatosis
Malignant Neoplasms Associated with Eosinophilia
Leukemia
Lymphoma
Lung cancer
Adenocarcinoma of various organs
Squamous cell carcinoma of various organs
Systemic Disease Associated with Eosinophilia
Postradiation pneumonitis
Rheumatoid arthritis
Sarcoidosis
Sjögren's syndrome

Acute eosinophilic pneumonia

- Acute eosinophilic pneumonia is an acute febrile illness (of less than 5 days' duration), characterised by diffuse pulmonary infiltrates and hypoxic respiratory failure., is often mistaken for (ARDS).
- the predominant symptoms of acute eosinophilic pneumonia are cough, dyspnea, malaise, myalgias, night sweats, and pleuritic chest pain, physical exam findings include high fevers, basilar rales, and rhonchi on forced expiration.
- HRCT : bilateral patchy ground-glass or reticular
- BAL, which demonstrates > 25% eosinophils
- Glucocorticoids invariably induce complete resolution.

CHRONIC EOSINOPHILIC PNEUMONIA

- Typically presents in an insidious manner with malaise, fever, weight loss, breathlessness and unproductive cough. It is more common in middle-aged females
- The classical chest X-ray appearance has been likened to thephotographic negative of pulmonary oedema with bilateral,peripheral and predominantly upper lobe parenchymal shadowing
- The peripheral blood eosinophil count is almost always very high,and the erythrocyte sedimentation rate (ESR) and total serumIgE are elevated.
- BAL reveals a high proportion of eosinophils
- Response to prednisolone is usually dramatic

Infectious Causes of Pulmonary Eosinophilia

Löffler Syndrome
Ascaris
Hookworm
Schistosomiasis
Heavy Parasite Burden
Strongyloidiasis
Direct Pulmonary Penetration
Paragonimiasis
Visceral larval migrans
Immunologic Response to Organisms in Lungs
Filariasis
Dirofilariasis
Cystic Disease
Echinococcus
Cysticercosis
Other Nonparasitic
Coccidioidomycosis
Basidiobolomycosis
Paracoccidioidomycosis
Tuberculosis

Infectious Causes of Pulmonary Eosinophilia

- Loffler syndrome
- refers to transient pulmonary infiltrates with eosinophilia that occurs in response to passage of helminthic larvae through the lungs, most commonly larvae of *Ascaris* species (roundworm).
- Symptoms are generally self-limited and may include dyspnea, cough, wheeze, and hemoptysis. Loffler syndrome may also occur in response to hookworm infection with *Ancylostoma duodenale* or *Necator americanus*

Tropical pulmonary eosinophilia

- occurs as a result of a mosquito borne filarial infection with *Wuchereria bancrofti* or *Brugia malayi*
- . The condition presents with fever, weight loss, dyspnoea and asthma-like symptoms.
- The peripheral blood eosinophilia is marked, as is the elevation of total IgE. High antifilarial antibody titres are seen. The diagnosis may be confirmed by a
- response to treatment with diethylcarbamazine (6 mg/kg/day for3 weeks).
- Tropical pulmonary eosinophilia must be distinguished from infection with *Strongyloides stercoralis* as, in strongyloidiasis, glucocorticoids may cause a life-threatening hyperinfection syndrome

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

- Allergic bronchopulmonary aspergillosis (ABPA) occurs as a result of a hypersensitivity reaction to germinating fungal spores in the airway wall.
- The condition may complicate the course of asthma and cystic fibrosis, and is a recognised cause of

pulmonary eosinophilia .

- The prevalence of ABPA is approximately 1–2% in asthma and 5–10% in CF.
- Genetic susceptibility is important

Clinical features

- Clinical features depend on the stage of the disease.
- Common manifestations in the early phases include fever, breathlessness, cough productive of bronchial casts and worsening of asthmatic symptoms.
- The appearance of radiographic infiltrates may cause

ABPA to be mistaken for pneumonia but the diagnosis may also be suggested by segmental or lobar collapse on chest X-rays of patients whose asthma symptoms are stable.

Features of allergic bronchopulmonary aspergillosis

- Asthma (in the majority of cases)
- Proximal bronchiectasis (inner two-thirds of chest CT field)
- Positive skin test to an extract of *Aspergillus fumigatus*
- Elevated total serum immunoglobulin E (IgE) >417 kU/L (1000 ng/mL)
- Elevated *A. fumigatus*-specific IgE or IgG
- Peripheral blood eosinophilia $>0.5\times10^{9}$/L
- Presence or history of chest X-ray abnormalities
- Fungal hyphae of *A. fumigatus* on microscopic examination of sputum

Management

- Systemic steriods
  - ABPA is generally considered an indication for regular therapy with low-dose oral glucocorticoids (prednisolone 7.5–10 mg daily).
- In some patients, itraconazole (400 mg/day) facilitates a reduction in oral glucocorticoids; a 4-month trial is usually recommended to assess its efficacy.
- The use of specific anti-IgE monoclonal antibodies is under consideration.

Drug-induced respiratory disease

Non-cardiogenic pulmonary oedema (ARDS)

- Hydrochlorothiazide
- Thrombolytics (streptokinase)
- IV β-adrenoceptor agonists (e.g. for premature labour)
- Aspirin and opiates (in overdose)

Non-eosinophilic alveolitis

- Amiodarone, flecainide, gold, nitrofurantoin, cytotoxic agents — especially bleomycin, busulfan, mitomycin C, methotrexate, sulfasalazine

Pulmonary eosinophilia

- Antimicrobials (nitrofurantoin, penicillin, tetracyclines, sulphonamides, nalidixic acid)
- Drugs used in joint disease (gold, aspirin, penicillamine, naproxen)
- Cytotoxic drugs (bleomycin, methotrexate, procarbazine)
- Psychotropic drugs (chlorpromazine, dosulepin, imipramine)
- Anticonvulsants (carbamazepine, phenytoin)
- Others (sulfasalazine, nadolol)

Pleural disease

- Bromocriptine, amiodarone, methotrexate, methysergide
- Induction of SLE — phenytoin, hydralazine, isoniazid

Asthma

- Pharmacological mechanisms (β-blockers, cholinergic agonists, aspirin and NSAIDs)
- Idiosyncratic reactions (tamoxifen, dipyridamole)

Radiotherapy

- The effects are cumulative.
- Acute radiation pneumonitis
- is typically seen within 6–12 weeks and presents with cough and dyspnea. This may resolve spontaneously but responds to glucocorticoid treatment.
- Chronic interstitial fibrosis may present several months later with symptoms of exertional dyspnoea and cough. Changes are often confined to the area irradiated but may be bilateral. Established post-irradiation fibrosis does not usually respond to glucocorticoid treatment. The pulmonary effects of
- radiation are exacerbated by cytotoxic drugs, phenomenon of 'recall pneumonitis'

Rare interstitial lung diseases

Disease	Presentation	Chest X-ray	Course
Idiopathic pulmonary haemosiderosis	Haemoptysis, breathlessness, anaemia	Bilateral infiltrates, often perihilar Diffuse pulmonary fibrosis	Rapidly progressive in children Slow progression or remission in adults Death from massive pulmonary haemorrhage or cor pulmonale and respiratory failure
Alveolar proteinosis	Breathlessness and cough Occasionally fever, chest pain and haemoptysis	Diffuse bilateral shadowing, often more pronounced in the hilar regions Air bronchogram	Spontaneous remission in one-third Whole-lung lavage or granulocyte macrophage–colony stimulating factor (GM–CSF) therapy may be effective
Langerhans cell histiocytosis (histiocytosis X)	Breathlessness, cough, pneumothorax	Diffuse interstitial shadowing progressing to honeycombing	Course unpredictable but may progress to respiratory failure Smoking cessation may be followed by significant improvement Poor response to immunosuppressive treatment
Neurofibromatosis	Breathlessness and cough in a patient with multiple organ involvement with neurofibromas including skin	Bilateral reticulonodular shadowing of diffuse interstitial fibrosis	Slow progression to death from respiratory failure Poor response to corticosteroid therapy
Alveolar microlithiasis	May be asymptomatic Breathlessness and cough	Diffuse calcified micronodular shadowing more pronounced in the lower zones	Slowly progressive to cor pulmonale and respiratory failure May stabilise in some
Lymphangioleiomyomatosis	Haemoptysis, breathlessness, pneumothorax and chylous effusion in females	Diffuse bilateral shadowing CT shows characteristic thin-walled cysts with well-defined walls throughout both lungs	Progressive to death within 10 yrs Oestrogen ablation and progesterone therapy of doubtful value Consider lung transplantation
Pulmonary tuberous sclerosis	Very similar to lymphangioleiomyomatosis, except occasionally occurs in men		

Thank you